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# British Journal of Anaesthesia

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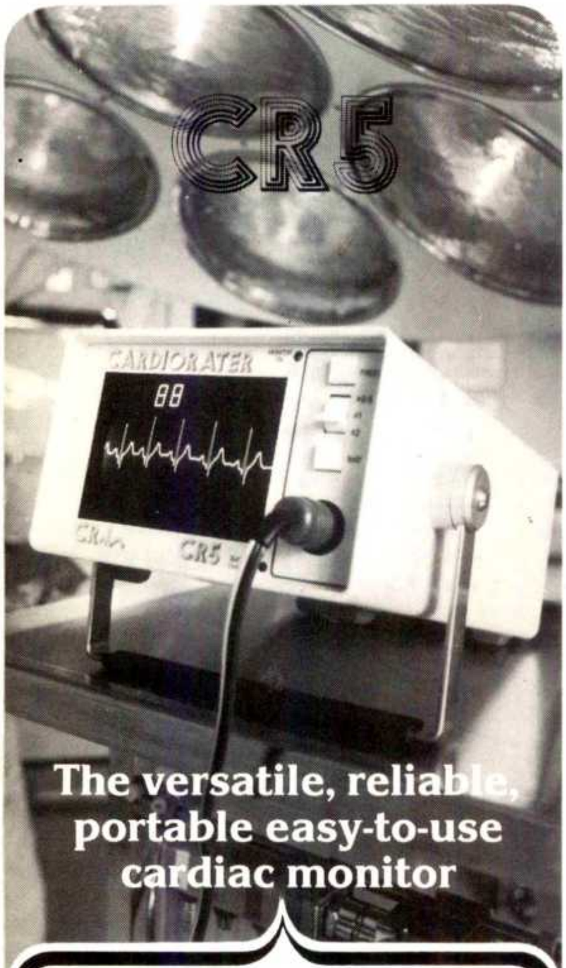

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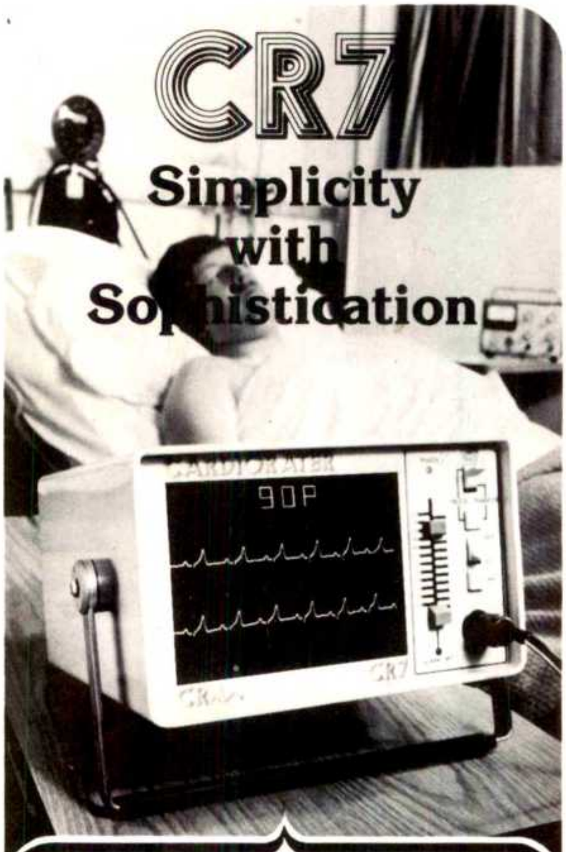

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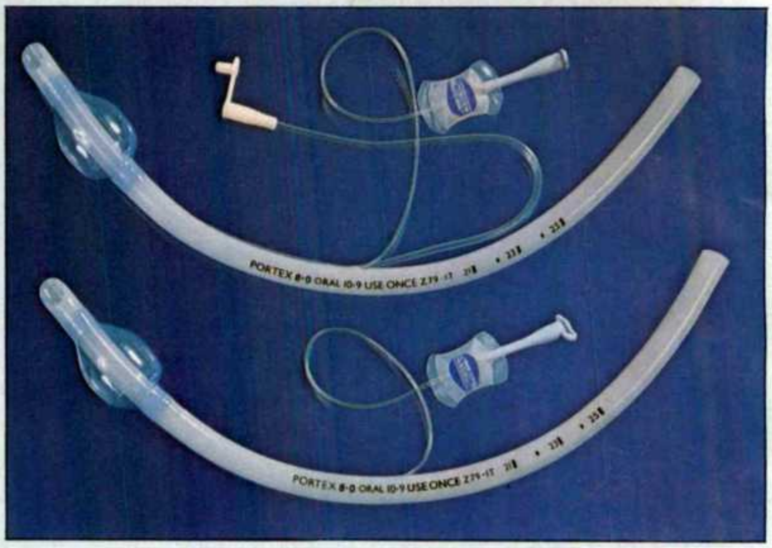
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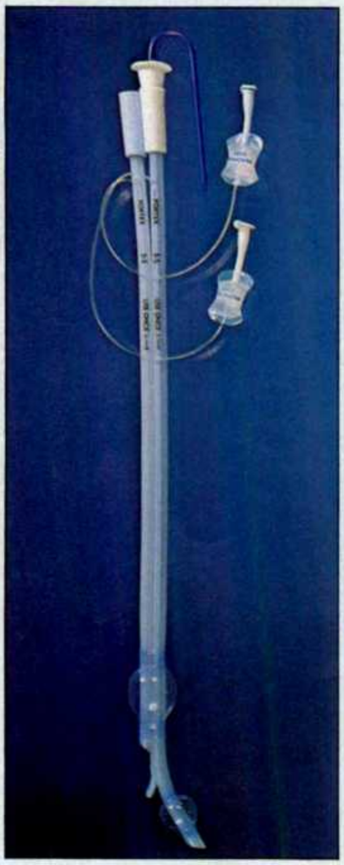

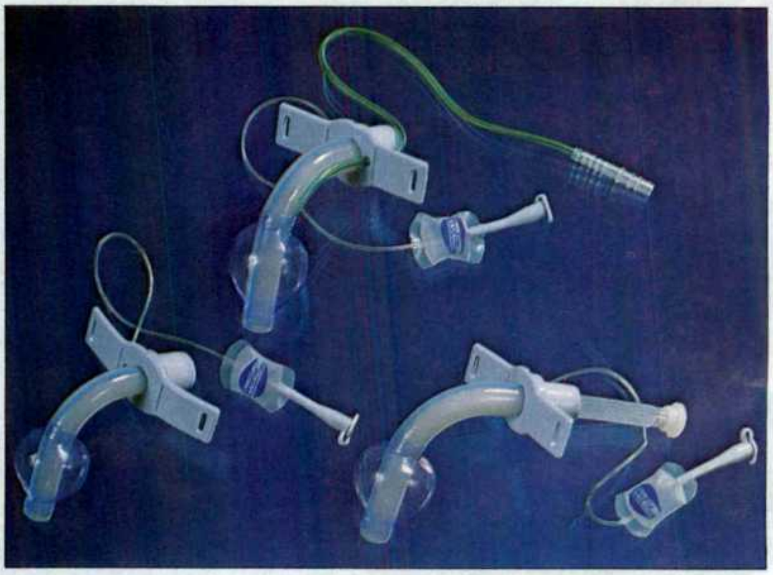

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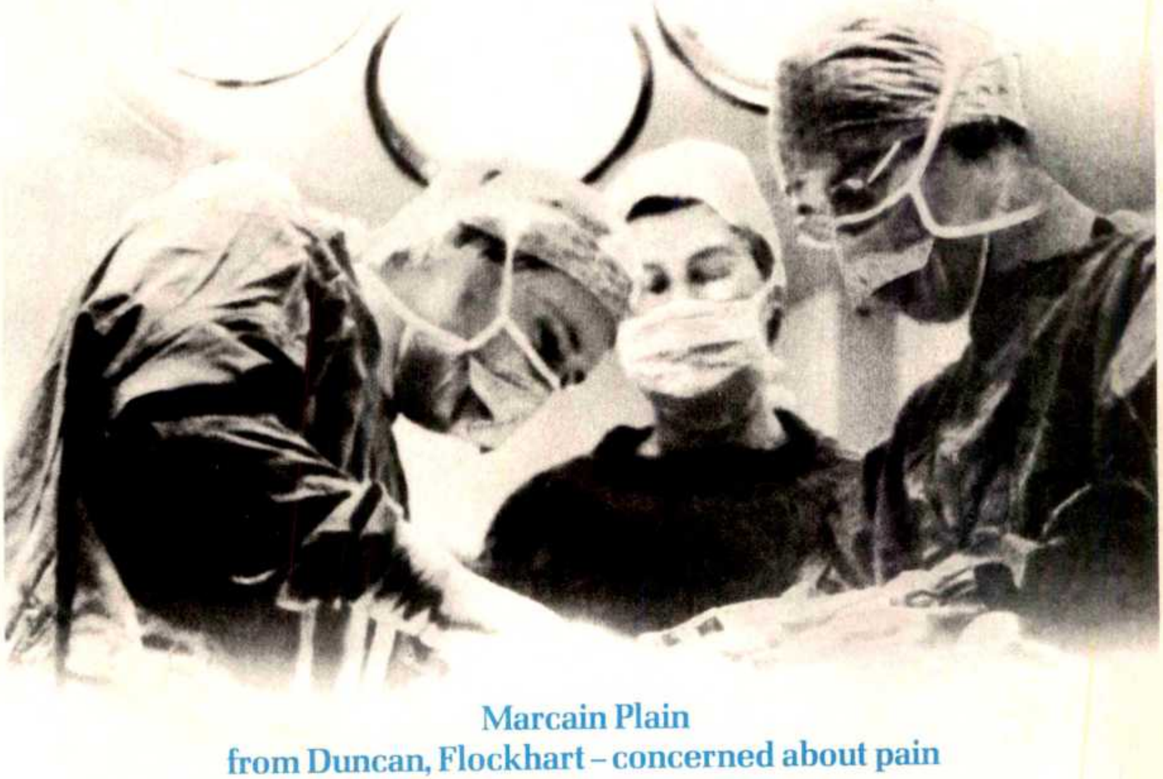

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**Prescribing information**

1. Moore DC 1979 "Regional Anesthesia Techniques" VI P34.

**Presentations, Product Licence numbers and Basic NHS cost** (exclusive of VAT).

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|---|---|---|
| 0·25% | 0021/5020 | 54·2p |
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|---|---|---|
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| 0·5% | 15–20 | 75–100 |
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See data sheet for recommendations for other blocks.

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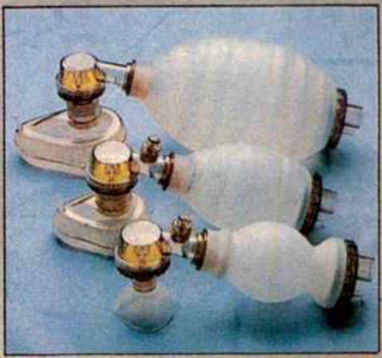

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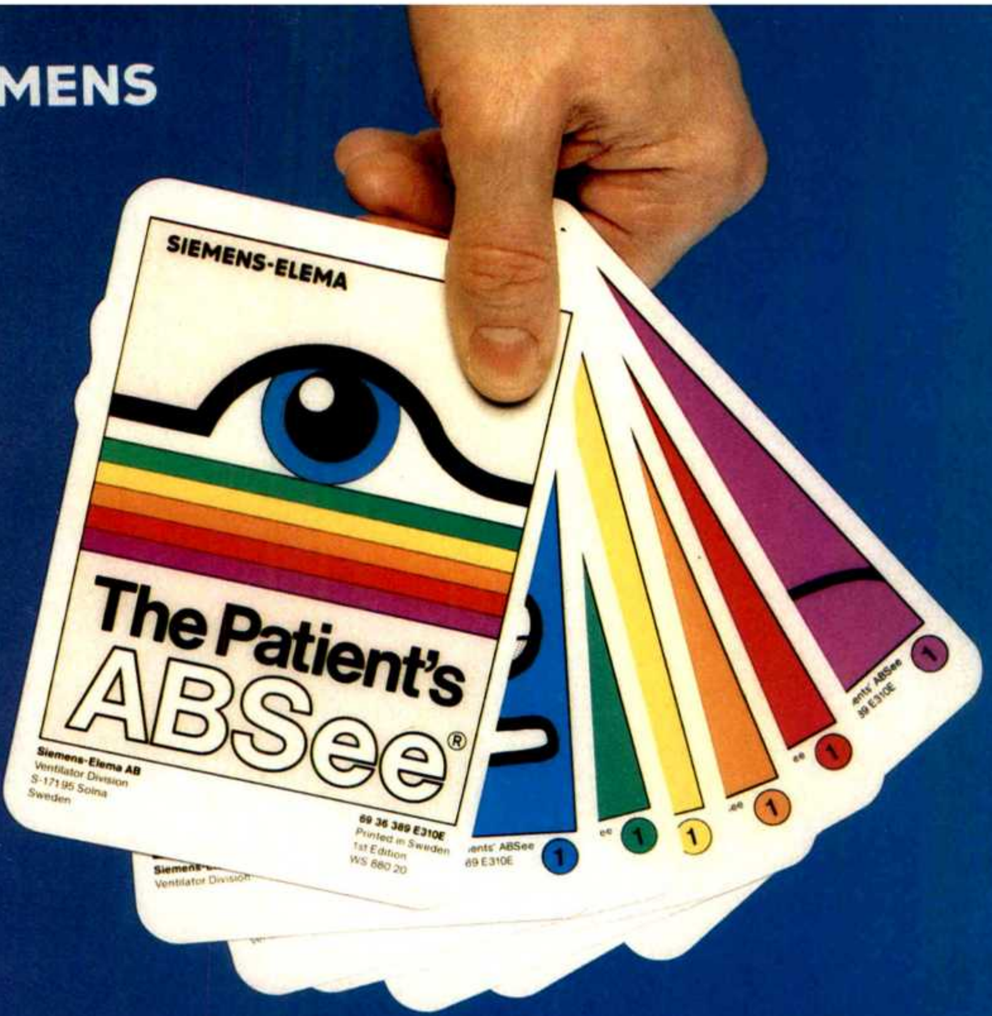

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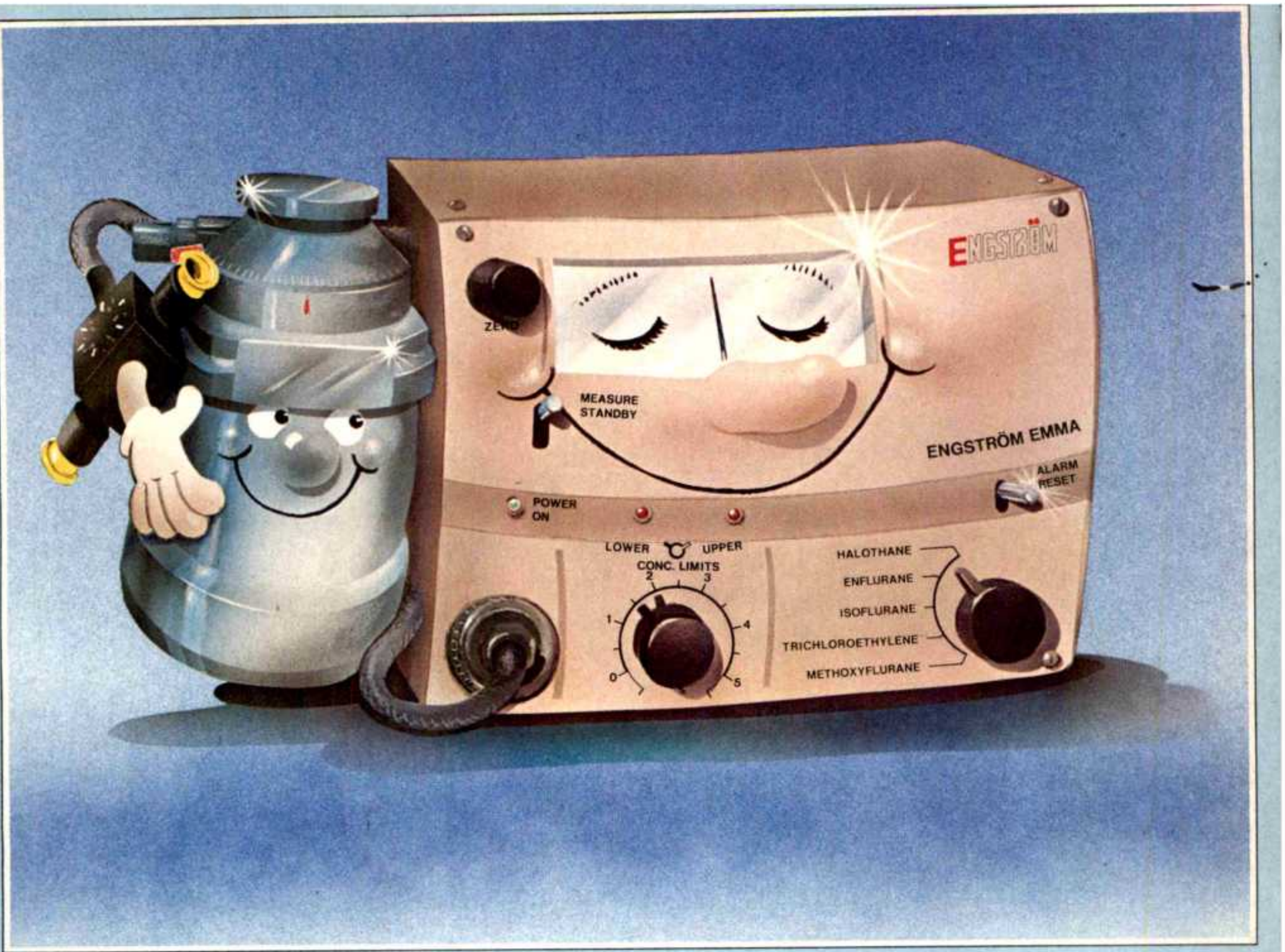

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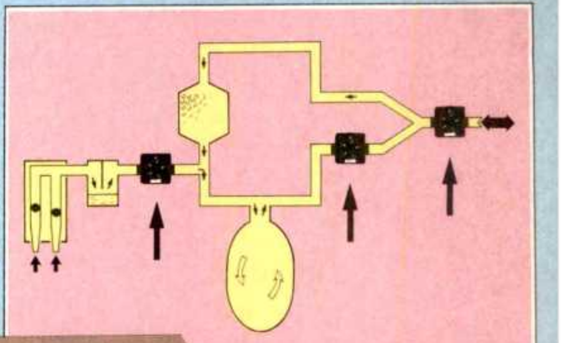
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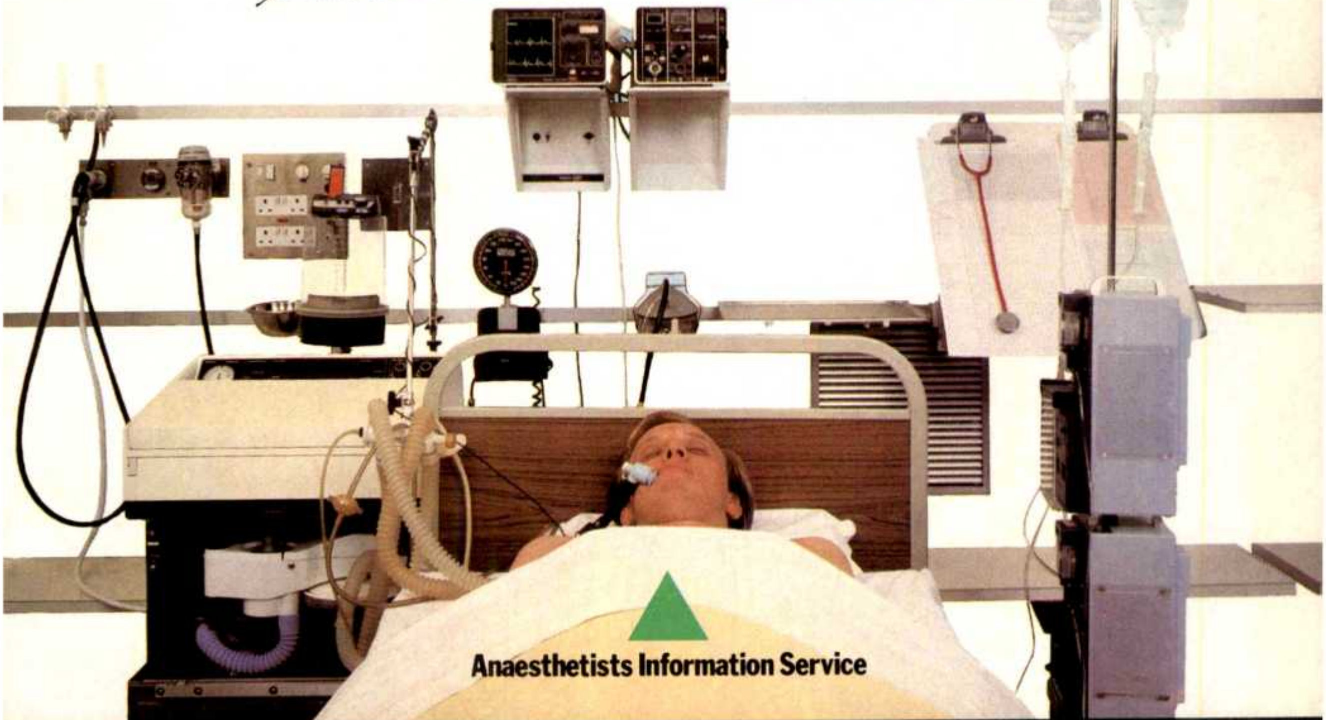

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BRITISH JOURNAL OF ANAESTHESIA

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# EDITORIAL

## THE ANAESTHETIST AND RESPIRATORY DYSFUNCTION

The respiratory disorders encountered in anaesthesia and intensive care continue to threaten the lives of patients and, in some cases, the longevity of the anaesthetists who struggle with these problems. Judged by the presentations at the Anaesthetic Research Society in recent years, however, there appears to be a paradoxical waning of interest in research into pulmonary dysfunction despite the ubiquity of these clinical problems. Has this occurred because the investigative tools are costly and complex and because the problems have become esoteric and obscure? Some of the tools are certainly complicated, but the problems themselves are clearly defined and in many cases are easily investigated using diagnostic equipment found in most general hospitals. The respiratory problems seen by anaesthetists include impaired function not only of the airway but also of the chest wall and lung parenchyma as well as abnormal regulation of breathing, and this issue reviews recent research into some of these problems. To avoid having to make critical comments both on the work of my North American colleagues and on my research group at Northwick Park, I will instead outline some of these problems from the standpoint of the clinical investigator and suggest how current research can be used to improve patient care.

A common and alarming problem during anaesthesia is loss of patency of either the intrapulmonary or the upper airway, but there are few studies in which these changes are quantified. The latest development in measuring intrapulmonary airway resistance ($R_{AW}$) in anaesthetized patients (Jordan et al., 1981) is technically complex but is quite simple in basic principle. It eliminates the effect on airway calibre of *unpredictable* change in lung volume by the simple manoeuvre of *deliberately* changing lung volume and measuring $R_{AW}$ continuously as volume changes. This method can be used to answer the question: "Are the infrequent but severe changes in $R_{AW}$ seen during anaesthesia only the tip of an iceberg and do large changes in $R_{AW}$ occur which are presently unrecognized?" With this question answered, the method provides the means to unravel the causes as well as quantifying the magnitude of change in $R_{AW}$ that complicates anaesthesia.

Another fascinating problem is to determine the factors which regulate the patency of the upper airway. Credit for launching a new attack on the pathophysiology of upper airway obstruction must go to physicians interested in the rare problem of obstructive sleep apnoea. Guilleminault and Dement (1978) have edited a superb symposium on sleep apnoea in which is described the use of fibreoptic endoscopy and electromyography of upper airway muscles to elucidate mechanisms of upper airway obstruction. Another technique to examine the upper airway is to produce a plot of upper airway cross-section as a function of the distance from the lips to the trachea by a non-invasive technique using high frequency acoustic reflections measured at the mouth (Fredberg et al., 1980). It has been shown that sleep causes a reduction in tone of upper airway musculature and not only the tongue but the muscular pharyngeal tube also may collapse inwards to occlude the airway. These changes are probably analagous to the changes in the upper airway during anaesthesia. An intriguing idea is that because a loss of patency of the upper airway is a result of reduced electrical activity in the muscles of this region, patency may be restored by external electrical stimulation of these muscles! That this problem is not confined to the rare sleep apnoea syndrome and to anaesthetized patients has been shown in our studies of patients during the 12-h period following anaesthesia (Catley et al., 1982). Central and obstructive apnoeas in these patients were very common when i.v. opiate was used to relieve pain, but also occurred without opiate in patients given regional analgesia after operation. Apnoeic periods occurred almost entirely during sleep and were associated with oxygen desaturation. When patients with obstructive airway disease fall asleep they may develop severe hypoxia associated with obstructive apnoea and this is associated with marked electrocardiographic changes (Tirlapur and Mir, 1982). In order to explain mysterious deaths following surgery, it is tempting to extrapolate these data to postoperative patients, although none of our patients had arterial oxygen saturations of less than 72%. It does emphasize, however, the need to reconsider the type of postoperative monitoring devices that would be acceptable if a higher standard of patient safety is to be achieved.

Not only the upper airway muscles but also the intercostals show marked impairment of function during sleep and anaesthesia. This loss of rib cage function may explain not only the impaired ventilatory response to carbon dioxide during sleep and anaesthesia (Jones, 1977; Cherniack, 1981), but also the loss of compensation to loaded breathing during anaesthesia. There is an extraordinary parallel between the effects of anaesthesia and, in particular, rapid eye movement sleep, in impairing rib cage and upper airway muscle function whilst sparing diaphragm function. This may be related to the remarkable lack of spindle control of the diaphragm compared with the rich spindle innervation of other muscles. The problem of fatigue of respiratory muscles during loaded breathing on conscious subjects has recently been outlined by Rochester (1981), but it is still not clear if diaphragmatic fatigue is more important than fatigue of non-diaphragmatic respiratory muscle. It is noteworthy, however, that anaesthetized and sleeping subjects who have impaired function of intercostal and upper airway muscle have very poor compensation to partial or complete obstruction of the airway.

A quite different clinical problem is posed by damage to the blood–gas interface in the lung which may result in the adult respiratory distress syndrome (ARDS). This can be considered in terms of (a) the vast number of different damaging agents, and (b) the early recognition of change in function of the interface consequent upon damage.

Reviewed in this issue are the deleterious effects of oxygen which may be manifest either as high altitude pulmonary oedema or high oxygen lung damage. It is not known whether the latter occurs by a direct effect of molecular oxygen or is mediated from the production within cells of the highly reactive free radicals such as superoxide anion, hydroxyl radical or singlet oxygen. It has also been proposed that the effects of increased concentrations of oxygen may be mediated by the release of these free radicals from neutrophils stimulated by increased oxygen to marginate to the walls of capillaries. There is certainly tremendous current interest in the release and cell-damaging effects of these free radicals produced by neutrophils (Weissmann, Smolen and Koichak, 1980) whether mobilized by oxygen, infections or immunologically-mediated processes (Jacob et al., 1980).

The new techniques described for measuring alveolar epithelial permeability described in this issue provide a number of methods for monitoring patients who may be susceptible to diffuse interstitial lung damage and ARDS. These techniques also provide the means for confirming the suggestions of Jacob and colleagues (1980) that complement activation with an increase in C5a may be an important mediator of diffuse lung damage in man. Patients can now be identified who have a considerable increase in permeability of the alveolar–capillary interface to hydrophilic solutes. If care is taken in these patients to minimize the hydrostatic pressure in the pulmonary capillaries then pulmonary oedema may be avoided. Furthermore, a diagnosis of increased permeability made at an early stage of the disease provides an opportunity to identify and prevent the effects of factors which increase lung permeability.

It is hoped that the application of some of these ideas may enable dramatic advances to be made in patient care and that the morbidity and mortality as a result of respiratory dysfunction in patients seen by the anaesthetists will become a distant memory.

*J. Gareth Jones*

## REFERENCES

Catley, D. M., Thornton, C., Jordan, C., Royston, D., Lehane, J. R., and Jones, J. G. (1982). Continuous post-operative monitoring reveals oxygen desaturation associated with paradoxical respiration. *Am. Rev. Respir. Dis.*, (in press).

Cherniack, N.S. (1981). Respiratory dysrhythmias during sleep. *N. Engl. J. Med.*, **305**, 27.

Fredberg, J. J., Wohl, M. E. B., Glass, G. M., and Dorkin, H. L. (1980). Airway area by acoustic reflections measured at the mouth. *J. Appl. Physiol.*, **48**, 749.

Guilleminault, C., and Dement, W. C. (eds) (1978). *Sleep Apnea Syndromes*, KROC Foundation Series, Vol. 11. New York: Liss.

Jacob, H. S., Craddock, P. R., Hammerschmidt, D. E., and Moldow, C. F. (1980). Complement-induced granulocyte aggregation: an unsuspected mechanism of disease. *N. Engl. J. Med.*, **302**, 789.

Jones, J. G. (1977). The chest wall—tone and movement. *Anesthesiology*, **47**, 325.

Jordan, C., Lehane, J. R., Jones, J. G., Altman, D. G., and Royston, J. P. (1981). Specific conductance using forced airflow oscillation in mechanically ventilated human subjects. *J. Appl. Physiol.*, **51**, 715.

Rochester, D. F. (1981). Is diaphragmatic contractility important? *N. Engl. J. Med.*, **305**, 278.

Tirlapur, V. G., and Mir, M. A. (1982). Nocturnal hypoxemia and associated electrocardiographic changes in patients with chronic obstructive airways disease. *N. Engl. J. Med.*, **306**, 125.

Weissmann, G., Smolen, J. E., and Koichak, H. M. (1980). Release of inflammatory mediators from stimulated neutrophils. *N. Engl. J. Med.*, **303**, 27.

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# THE PHYSIOLOGY OF LEAKY LUNGS

J. G. JONES, B. D. MINTY AND D. ROYSTON

This paper outlines the relationships between the structures and functions of the pulmonary epithelium and endothelium, and describes some new methods for measuring their permeability in a variety of experimental and clinical situations. Much of the work outlined in this paper is reviewed by Davies (1973), Staub (1974, 1978, 1981), Effros (1978), Staehelin and Hull (1978), Diana and Fleming (1979), and Chinard (1980).

Diffuse injury of the alveolar epithelium and the pulmonary vascular endothelium may follow aspiration of gastric contents, inhalation of toxic smokes and vapours or pulmonary embolism. Similar damage may occur when the complement system is activated during haemodialysis and after trauma or infection (Hammerschmidt et al., 1980). Complement activation has also been reported after cardiopulmonary bypass (Chenoweth et al., 1981) but no correlation was found between activation and changes in arterial oxygen tension. If any injury does occur it may cause these layers to become unduly leaky to water and solute. If the injury creates "holes" in the epithelium large enough to leak protein then pulmonary oedema will ensue, but if the leakage is minimal and confined to small molecular weight solutes there is no clinically obvious effect.

A major problem in establishing the link between a potentially damaging stimulus and this minimal pulmonary response has been the lack of an objective test to measure a deterioration in function of the vascular endothelium and, in particular, the epithelial lining of the airways and alveoli. Measurements of changes in lung mechanics or gas exchange are either non-specific or too insensitive to draw any conclusions about the functional effects of this minimal lung injury. One approach could examine the effect of lung injury on pulmonary metabolism (Said, 1979) but, so far, little is known about the effects of lung injury on this aspect of lung function (Hollinger et al., 1980).

A more direct approach is to quantitate the functional effects on the lung by measuring changes in permeability to water and solute of the lining layers of the lungs. The rate of flow of water and solute through a membrane is called the flux, when flow is divided by membrane area. The permeability of the membrane ($K$) is the flow of tracer molecules per unit area divided by the concentration difference of solute across the membrane. In practice the flow of labelled tracer molecules can be measured fairly easily, but the area of the lung membrane and the magnitude of the concentration difference is unknown. Consequently an "apparent" permeability coefficient or permeability "index" is used to describe the leakiness of the interface between the alveoli and pulmonary capillaries.

Within the past few years there has been an enormous growth of interest in studying lung permeability, although the basic physiological concepts were described many years ago. In 1896 Starling studied the vascular absorption of fluids from connective tissue spaces into small vessels. His hypothesis is summarized in figure 1 and in the equation:

$$\text{Net fluid flux} = K(\Delta P - \Delta\pi) \qquad (1)$$

where $K$ is the permeability of the wall, $\Delta P$ is the hydrostatic pressure gradient and $\Delta\pi$ is usually the protein osmotic pressure gradient across the wall. However, when the vessel or airway wall becomes very leaky to solute, that is when the leaks are large enough to permit protein to cross the wall, the osmotic pressure gradient, $\Delta\pi$, disappears, $K$ increases and fluid flux is dependent now only on $K$ and $\Delta P$:

$$\text{Net fluid flux} = K\Delta P \qquad (2)$$

When this happens the only clinical measures that can be instituted to reduce the risk of pulmonary oedema are to minimize $\Delta P$ and to attempt to reduce permeability.

In clinical practice a very large increase in pulmo-

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J. G. JONES, M.D.; B. D. MINTY, M.I.BIOL.; D. ROYSTON, M.B., F.F.A.R.C.S; Division of Anaesthesia, Clinical Research Centre, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ.

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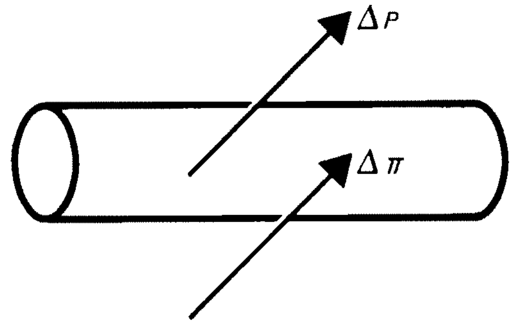

FIG. 1. The Starling equation describes net fluid flux across a vessel wall in terms of $K$, the permeability coefficient of the wall, $\Delta P$, the hydrostatic pressure gradient and $\Delta\pi$, the osmotic pressure gradient.

nary permeability can be inferred by demonstrating (a) radiographic pulmonary oedema, (b) normal plasma proteins and (c) normal pulmonary vascular pressures. It is confirmed by finding an increased protein concentration in pulmonary oedema fluid (Fein et al., 1979b). Thus the presence of radiographic pulmonary oedema is required before changes in lung leakiness in man can be diagnosed by excluding hypoprotinaemia and pulmonary capillary hypertension. This will be referred to later as the "exclusion method".

Techniques are now being developed which, in the absence of radiographic pulmonary oedema, can be used to demonstrate early changes in lung epithelial and endothelial permeability in man. In this paper the background to these techniques begins with an account of the structure of the alveolar–capillary interface. We then describe some of the original studies on lung permeability in animals, and give an account of permeability-type pulmonary oedema in man. We conclude with a description of techniques that may be of use in measuring lung permeability in man.

## THE NORMAL ALVEOLAR-CAPILLARY INTERFACE

### *Structure of the interface*

The normal lung permits a rapid, bi-directional diffusion of gas molecules across the interface between pulmonary capillary blood and the alveolar space. This interface is thin enough to permit rapid gaseous diffusion but, because it is a semipermeable membrane, the balance of hydrostatic and osmotic forces prevents the filtration of water and solute from the blood and interstitial space into the alveoli. The interface is made up of at least two layers of cells which are quite different, in both structure and function. The alveolar epithelium and the capillary endothelium are separated to varying degrees by an interstitial space which contains connective tissue and the lymphatic system of the lung. As much as 95% of the alveolar surface area consists of a layer of type I cells which form thin flat sheets 0.1–0.3 μm in thickness. The type II cells produce surfactant, are mainly responsible for repair following pulmonary epithelial damage and occupy quite a small part of the alveolar surface area. The basement membranes of the alveolar epithelium and capillary endothelium are in contact only in some parts of the alveolar–capillary interface which form the thinnest part ($< 0.5$ μm) of the interface. Elsewhere the two basement membranes are separated by the interstitial space in the thick portion of the interface ($> 1.0$ μm). The endothelial cells which line the pulmonary capillaries are unremarkable on ultramicroscopic examination, but this belies their fundamental role in the metabolism of angiotensin I, bradykinin, prostacyclin and factor VIII (Said, 1979).

It is important to remember that the permeability to water and solutes of the pulmonary vascular endothelium is very much greater than that of the alveolar epithelium. In the following sections we will discuss the evidence for this large difference in permeability.

### *Structure and function of cell membranes*

The outer membrane of a cell consists of a bilipid layer containing proteins, cholesterol and glycoproteins which interlock to form a mosaic 6–12 nm in thickness ($1\ \text{nm} = 10^{-9}\ \text{m} = 10\text{Å}$). The main function of this membrane is to exclude some molecules from the cell and to permit others to permeate, either passively or actively, in or out of the cell.

Passive transport depends on the physical properties of the molecule and the concentration and electrical gradients across the plasma membrane. For example, non-polar molecules have a high lipid solubility and low solubility in water (lipophilic molecules) and pass easily through the membrane. Ionic polar compounds are electrolytes, and the greater is the ionization the greater is the solubility in water (hydrophilic molecules). Normally hydrophilic molecules are excluded from the cell by the bilipid layer. Some cells, however, have protein molecules in the membrane arranged in the form of channels which permit a limited number of small hydrophilic molecules to diffuse through.

Active transport is an energy-dependent mechanism which includes: endo- and exo-cytosis in which the cell membrane forms a vesicle which carries the molecule either into or out of the cell, one-way pumps and exchange pumps. All of these mechanisms serve to transport molecules not only in and out of individual cells but also across whole sheets of cells such as the epithelium and endothelium. Since the osmolality on both sides of cell membranes must be equal, water will distribute according to the amount of solute on either side of the membrane.

There is no reason to believe that the large differences in permeability of the alveolar epithelium and pulmonary vascular endothelium can be explained by differences in the cell membranes of these layers. This important difference in permeability to hydrophilic solutes is almost certainly a result of the different intercellular junctions in the two cell types.

### *Intercellular junctions*

Normally there is a gap between cells with is about 2–6 nm in width. However, it would be of little value if energy were consumed to transport molecules across, say, an epithelial layer if the same molecules could then passively diffuse back through the intercellular gaps. To prevent this happening adjacent cell walls are joined in a number of locations by one or other of three functional categories of intercellular junctions. These are ***tight***, ***adhering*** or ***communicating*** junctions (Staehelin and Hull, 1978). Tight junctions are relatively impermeable and are particularly important in epithelial layers but are also found in vascular endothelia. In freeze fracture studies the tight junction is characterized by a network of ridges composed of two rows of tightly packed membrane proteins with complementary grooves on the cell membrane of the adjacent cell. These proteins form lines of attachment called the sealing strands. The greater the number of sealing strands the more impermeable is the junction. Inoue, Michel and Hogg (1976) and Schneeberger and Karnovsky (1976) showed that the alveolar epithelial cells were joined by multiple strands, whereas the pulmonary endothelial cells were connected by only one or two sealing strands which were discontinuous in some regions. They showed that electron-dense tracers such as horseradish peroxidase (mol. wt. 40 000 daltons, molecular radius ≈ 3 nm) can diffuse through the endothelium into the interstitial space, but not through the alveolar epithelial junctions.

It is generally believed that the intercellular junctions are the main site of hydrophilic solute permeation through cell layers. We will refer to these sites as "equivalent pores" and in the next section will describe the original studies which first showed that the equivalent pores in the alveolar epithelium are very much smaller than those in the pulmonary vascular endothelium.

### *How permeable is a semi-permeable membrane?*

A membrane which lets a solvent such as water pass through but not a solute (for example glucose) is called a semi-permeable membrane. A simple osmometer is shown in figure 2.

The water in the beaker is separated from the solute by a semi-permeable membrane. At equilibrium the osmotic pressure ($\pi$) pushing solute up the tube is exactly balanced by the hydrostatic pressure in the tube. The permeability of a perfect semi-permeable membrane to the solute is zero, which implies that the pore size of the membrane is too small to permit the individual molecules of the solute to pass through. In practice the membrane is not perfect and allows some molecules of the solute to leak slowly through so that the actual osmotic pressure ($\pi^1$) is less than the ideal ($\pi$). The ratio $\pi^1/\pi$ is called the ***reflection coefficient*** ($\sigma$). The reflection coefficient for a given membrane tends to decrease with decreasing molecular weight of solute. Knowledge of the reflection coefficient of a membrane for any solute will indicate the actual osmotic pressure that may be achieved across that membrane for a given concentration gradient of that solute. We can

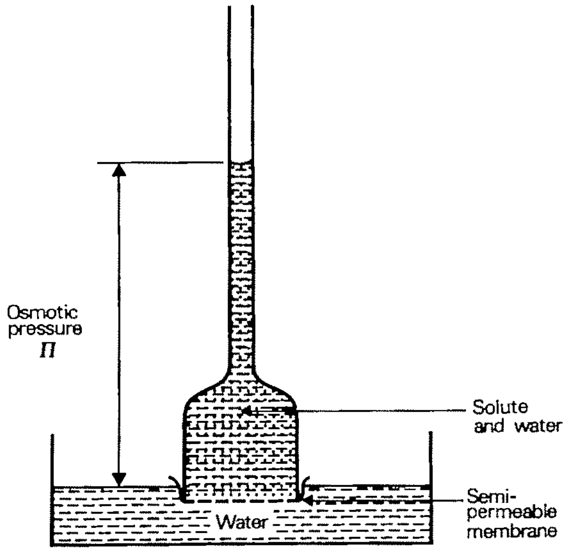

FIG. 2. A simple osmometer showing that at equilibrium the osmotic pressure is equal and opposite to the hydrostatic pressure.

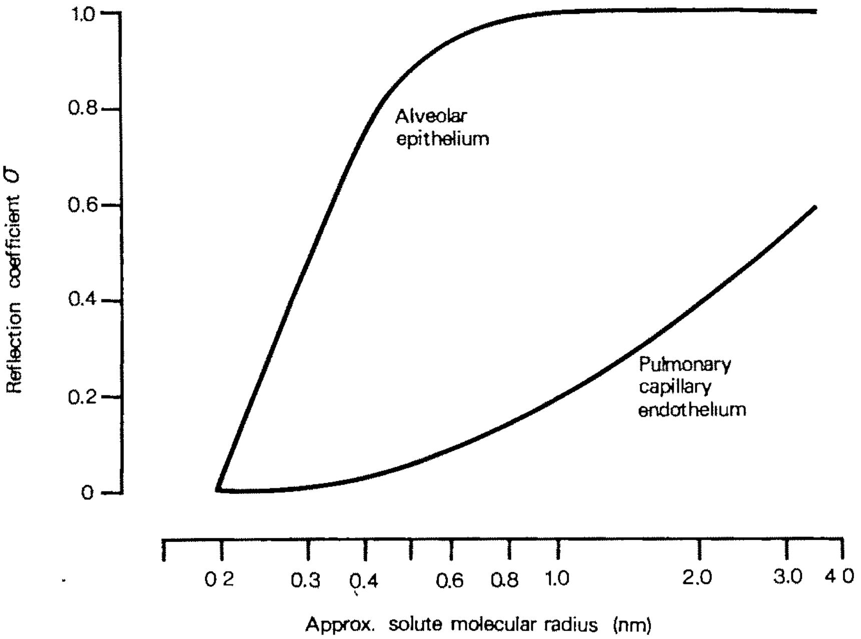

FIG. 3. The reflection coefficients $\sigma$ of alveolar epithelium and pulmonary capillary endothelium for a range of hydrophilic solutes. The relationship between molecular weight and the approximate solute molecular radius is shown in table I.

now modify the Starling equation to take into account the effect on the osmotic pressure gradient of changes in reflection coefficient:

$$\text{Net fluid flux} = K(\Delta P - \sigma\Delta\pi) \quad (3)$$

Taylor and Gaar (1970) showed how the reflection coefficient for a membrane depends upon the molecular radius of different solute particles passing through the membrane. It can be seen that $\sigma$ for the alveolar epithelium increases to 1.0 when solute particle radius exceeds 0.8 nm (fig. 3) whereas, with the same solute, $\sigma$ for the capillary endothelium is 10 times less (about 0.1). The $\sigma$ of the alveolar epithelium for protein is 1.0 whereas $\sigma$ for the pulmonary endothelium for protein is probably less than 0.6. Taylor and Gaar (1970) also showed that the pore radii of the alveolar epithelium were 0.8–1.0 nm and the pulmonary capillary endothelium was 4.0–8.0 nm.

TABLE I. *Relationship between molecular weight and approximate molecular radius*

| Substance | Mol. wt. | Approx. radius (nm) |
|---|---|---|
| Water | 18 | 0.15 |
| Sodium chloride | 58 | 0.23 |
| Urea | 60 | 0.26 |
| Glucose | 180 | 0.37 |
| Sucrose | 340 | 0.48 |
| Tc-DTPA | 492 | 0.57 |
| Myoglobin | 17000 | 1.90 |
| Albumin | 67000 | 3.60 |

The relationship between molecular weight and the approximate molecular radius of various substances of interest is shown in table I.

### *Magnitude of the hydrostatic and osmotic pressure gradients*

So far we have looked at a simple version of the Starling equation and suggested that a change in the reflection coefficient, $\sigma$, modifies the effective osmotic pressure gradient. It must be emphasized that there is considerable uncertainty about the magnitude of the hydrostatic and oncotic pressure gradients across the alveolar–capillary interface. Although the pulmonary artery wedge pressure gives an index of pulmonary microvascular pressure, the pressure outside the vessel is unknown and is assumed to be normally rather small, about 1 mm Hg. Similarly, the colloid osmotic pressure of blood can be measured, but osmotic pressure of interstitial space fluid is not known with any certainty. Because of the leakiness of the capillary endothelium to all but large molecules, it is usual to consider only the protein contribution to the gradient at this location. The protein concentration of pulmonary interstitial fluid (lung lymph) may exceed 50% of that in plasma. In contrast to that of the endothelium, the reflection coefficient of the alveolar epithelium is quite high even for ions as small as sodium chloride and urea (fig. 3, table I). Consequently a very much larger osmotic gradient can be obtained across the alveolar epithelium.

We will now consider the remaining term in the Starling equation, the coefficient $K$. This is considered in two parts, the fluid filtration coefficient ($K$f) and the permeability coefficient for solute ($w$i). These are measured in different ways but, for small molecular weight solutes, an increase in $w$i is inevitably accompanied by an increase in water flow because, as we have pointed out above, water and solute flow are interdependent. Because it is technically easier to measure $w$i in man this is often used as an index of $K$f.

### *Apparent fluid filtration coefficient (Kf)*

The transudation rate of water, expressed as the fluid filtration coefficient ($K$f), is the flow rate of water from the pulmonary capillaries through the whole alveolar epithelial area. It was first determined experimentally by Guyton and Lindsey (1959) who increased left atrial pressure and measured the accumulation of lung water by postmortem analysis of lung weight. In animals with normal plasma proteins they found no fluid accumulation until left atrial pressure reached a critical value of 23 mm Hg (fig. 4).

Above this pressure the rate of transudation of water into the alveoli was 0.21 ml mm $\mathrm{Hg}^{-1}\mathrm{h}^{-1}$ per gram of lung. The rate of fluid accumulation is unaffected by plasma protein concentration, being determined only by the porosity of the epithelium to water. A reduction in plasma protein concentration shifts the curve to the left so that transudation begins at a lower microvascular pressure (fig. 4).

### *Apparent permeability coefficient for solute, wi*

Since the epithelial and endothelial layers have different reflection coefficients they must also have different permeabilities to the different molecular weight solutes that tend to pass through them. The permeability coefficient ($w$i) of a membrane to a solute molecule, i, is the solute flux per unit membrane area divided by the concentration difference.

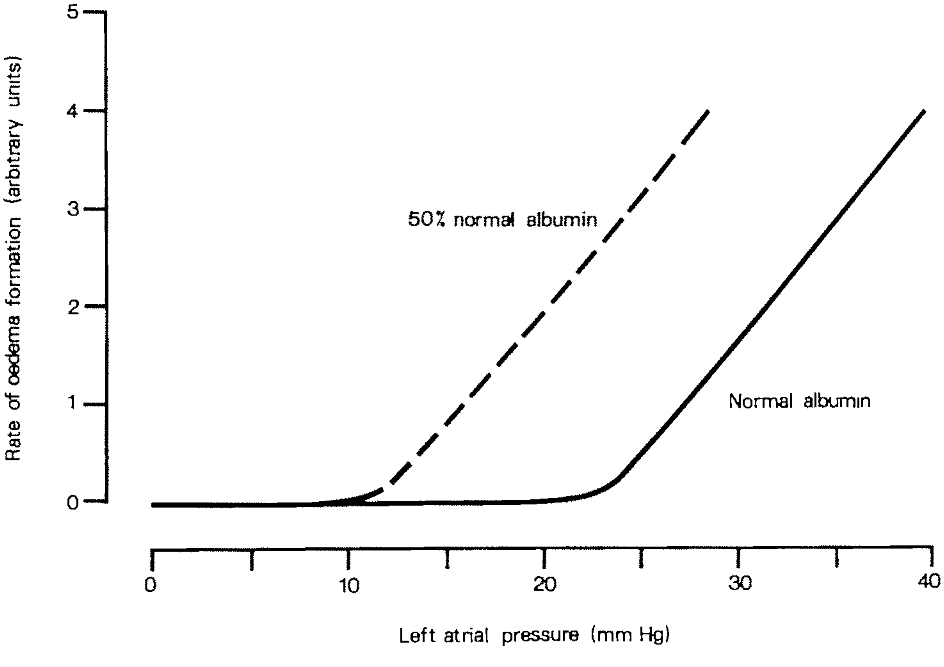

FIG. 4. The critical left atrial pressure for fluid flux into the alveoli is 23 mmHg. This critical pressure decreases when plasma colloid osmotic pressure decreases. The slope of the line is the fluid filtration coefficient ($K$f).

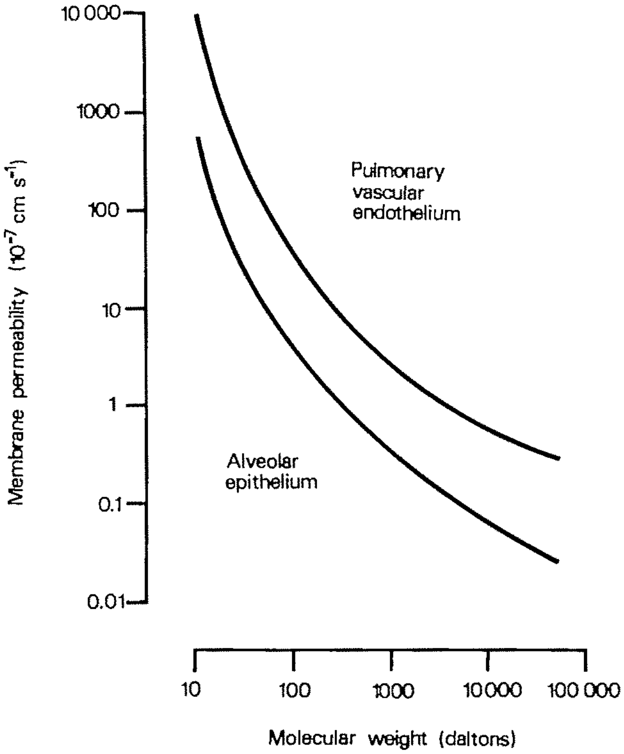

FIG. 5. For normal lungs the permeability coefficients of the pulmonary vascular endothelium are about 10 times greater than those of the alveolar epithelim over the range of molecular weights studied. (Data from Staub, 1974.)

Taylor, Guyton and Bishop (1965) first calculated *wi* in isolated perfused lungs with the alveoli filled with liquid, from the expression:

$$wi = \frac{0.693 \cdot V_V \cdot V_A}{T_{\frac{1}{2}} \cdot A(V_V + V_A)} \qquad (4)$$

where *wi* is permeability coefficient (cm $s^{-1}$), $V_V$ and $V_A$ are the volumes of fluid in the vascular and alveolar compartments (ml), $A$ is the surface area of alveoli (662 $cm^2$ per gram weight of air filled lung). $T_{\frac{1}{2}}$ is the half-time clearance of tracer from $V_V$ to $V_A$, and is usually measured using a radiolabelled tracer.

The solute permeability can be derived for either the alveolar epithelium or the capillary endothelium. Staub (1974) has reviewed the published permeability coefficients for each of these layers for a range of different molecular weight solutes (fig. 5). Over the range of molecular weights studied, the permeability of the endothelium was at least 10 times greater than that of the epithelium. This difference is not necessarily fixed because the permeability can increase in a variety of experimental and pathological conditions.

### *Relationship between Kf, wi and $\sigma$*

The flux of solute through the membrane takes place in two ways, by molecular diffusion through small pores or by bulk flow (convective flow) through large pores. Strictly speaking, the permeability of a membrane to solute, i, should be calculated only for diffusive flow, that is when bulk flow is zero (Staub, 1974). The equation (5) relates solute flux to solute permeability coefficient (*wi*), mean concentration of solute passing through the membrane ($\bar{C}$) and water flux ($Q$f):

$$\text{Solute flux} = \underbrace{wi \cdot A \cdot \Delta\pi}_{\text{Diffusion of solute}} + \underbrace{(1-\sigma)\bar{C} \cdot Q\text{f}}_{\text{Bulk flow of solute}} \qquad (5)$$

The likelihood of bulk flow is indicated from the magnitude of the reflection coefficient. The bigger the pores the smaller is $\sigma$ and the greater is bulk flow. Conversely, with an almost perfect semi-permeable membrane $\sigma$ approaches 1, so that $(1-\sigma)$ approaches zero and bulk flow ceases, solute flux under these circumstances occurring only by diffusion.

Because an increase in both the number and size of pores is likely to increase both $Kf$ and $wi$, the magnitude of the fluid filtration coefficient ($Kf$) may be inferred from the magnitude of the solute permeability, $wi$. As suggested by figure 3, processes that produce a gradual increase in the pore size of alveolar epithelium will result in an increase in leakage of water and small molecular weight solutes long before there is an increase in protein flux.

The studies of Egan (1980) support this view by showing that when the lung is overdistended there is an increase in permeability of the alveolar epithelium because of an increase in mean pore size. This caused an increased flux of sucrose (0.5 nm) but not solutes larger in molecular size than inulin (1.4 nm). This may have implications for patients treated with high end-expiratory pressures.

In the next section will be described the functional consequences of changes in the various parameters in the Starling equation.

*Leakage of water and solute*

For flux through the vascular endothelium, the Starling equation predicts the effect of varying the microvascular pressure, the reflection ($\sigma$) and permeability coefficients ($Kf$) (fig. 6). It is assumed that plasma protein concentration is constant; the baseline value of $\sigma$ is 0.6; the gradient of colloid osmotic pressure is 12 mm Hg and $Kf$ is 1. Using these values a net outward flux from the capillary begins at a critical microvascular pressure of about 7 mm Hg. Changes in $Kf$ and $\sigma$ change the flux rate and the critical pressure. This critical microvascular pressure for outward flux through the endothelium is clearly much smaller than that for flux through the alveolar epithelium (23 mm Hg). As microvascular pressure increases towards 23 mm Hg it is likely that the fluid flux into the interstitial space causes an increase in interstitial space pressure. If the Starling equation is now applied across the alveolar epithelium, $\Delta P$ corresponds to the pressure difference between the alveolar lumen and interstitial space. In these circumstances $\sigma$ for the epithelium is 1 and $\Delta\pi$ is now the osmotic pressure difference between the alveolar lining liquid and interstitial space liquid.

Bearing in mind that although $Kf$ for the epithelium may be 10 times smaller than for the endothelium, the effect of changing $Kf$ and $\sigma$ for the alveolar epithelium will have the same kind of effect on critical pressure and fluid flux as that seen for the endothelium.

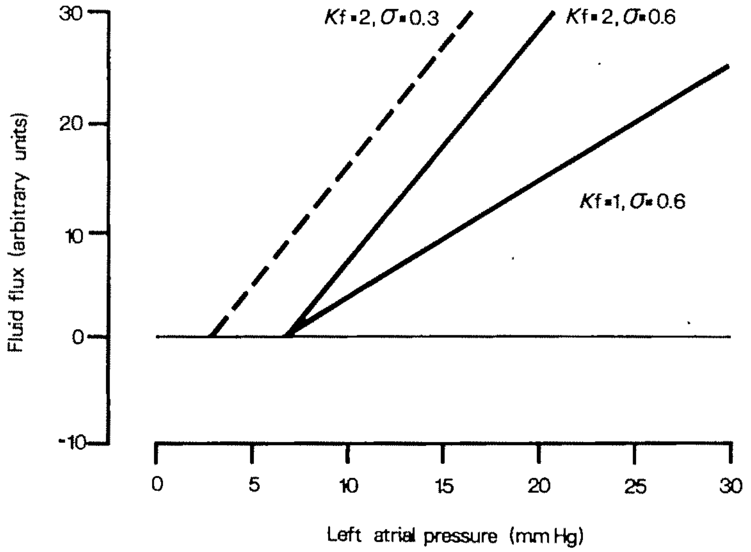

FIG. 6. The Starling equation applied to the pulmonary capillary endothelium (see text). The effect of increasing $Kf$ is to increase the fluid flux. Reduction of $\sigma$ shifts the curve to the left and reduces the critical pressure for fluid flux. The same type of relationship holds for the alveolar epithelium, but the critical pressure is much greater (23 mmHg). (See fig. 4.)

Permeability pulmonary oedema results from a large increase in epithelial pore size accompanied by a similar increase in *Kf* and *wi* and a decrease in $\sigma$. As $\sigma$ for protein decreases to zero a massive water and protein flux into the alveolar space can be prevented only by decreasing the intravascular pressure with diuretics and peripheral vasodilator drugs. Some of the causes of permeability type pulmonary oedema are shown in table II.

## THE "EXCLUSION" METHOD FOR MEASURING LUNG PERMEABILITY IN MAN

We showed in the introduction that, until recently, an increase in lung permeability could be deduced only in the presence of pulmonary oedema by excluding pulmonary microvascular hypertension and a low plasma oncotic pressure. In this section we will look more closely at this "exclusion method" by reviewing the sensitivity of methods for measuring lung water.

An increase in lung water may be inferred from:

*Clinical signs.* Dyspnoea, cough, frothy sputum and crepitations are the cardinal symptoms and signs. Chait and others (1972) pointed out that, of 31 patients with radiological pulmonary oedema, none had these signs or symptoms.

*Chest radiographs.* Clinically, pulmonary oedema is diagnosed almost exclusively in this way, but the sensitivity of the technique has been questioned by many workers. As much as an 80% increase in lung water may be necessary before the radiograph shows changes of pulmonary oedema (Snashall, 1980).

More sensitive methods may be:

*Lung function tests.* A decrease in vital capacity and changes in static compliance may occur, but are unreliable and non-specific. Oedema foam in the alveoli probably does not contribute to the changes in lung mechanics (Grossman, Jones and Murray, 1980). Closing volume has been reported to increase in patients with pulmonary oedema but Jones, Lemen and Graf (1978) have shown that this effect may occur as a result of vascular distension in the absence of an increase in lung water and is reversed by vagal blockade.

*Electrical impedence.* Severinghaus, Catron and Noble (1972) developed a "focusing" system of electrodes to eliminate the effects of the chest wall on transthoracic impedance, but this method has not achieved sufficient accuracy for clinical use. Fein and others (1979a) evaluated a simpler system and found no greater sensitivity than the chest radiograph.

TABLE II. *Factors associated with permeability-type pulmonary oedema*

| | |
|---|---|
| Inhalation: | Gastric contents |
| | Fire smoke |
| | Oxygen |
| | Nitrogen dioxide, nitric oxide |
| | Ozone |
| | Acrolein |
| | Phosgene |
| Drugs, poisons: | Bleomycin |
| | Busulphan |
| | Nitrofurantoin |
| | Heroin |
| | Alloxan |
| | Paraquat |
| | Drug hypersensitivity |
| Miscellaneous: | ARDS |
| | Septicaemia (Gram negative) |
| | Fat, air embolism |
| | Uraemia |
| | Goodpasture's syndrome |
| | High altitude oedema |
| | Neurogenic oedema |
| | Complement activation |

*Lung density.* An increase in lung water may be demonstrated using computerized axial tomography (Kreel, personal communication). A variety of other methods of measuring the effect of lung density on absorption of radiation are reviewed by Staub (1974).

*Soluble gas uptake.* Attempts have been made to develop the soluble gas uptake method of Cander and Forster (1959) to measure lung water. The problem here is that the technique cannot detect water in non-ventilated parts of the lung (Jones and Milledge, 1980).

*Indicator dilution curves.* This involves the measurement of the transit times of two indicators injected simultaneously into the pulmonary artery. One of these indicators remains in the lung vasculature while the other is a diffusible indicator that can pass through the endothelial wall into surrounding water. The difference in transit time is a function of the water volume into which the diffusible indicator passes. A major technical problem arises where arterial blood must be sampled rapidly into a series of discrete tubes. This difficulty may be overcome by using a bolus of cold saline as the diffusible indicator and indocyanine green as the non-diffusible indicator. This technique lends itself to on-line computer calculation of lung water (Lewis and Elings, 1978). Objections have been raised to this technique in that it tends to overestimate lung water. All of these indicator dilution techniques are sensitive to a change in pulmonary perfusion, so that an apparent increase in lung water may simply be a result of an increase in pulmonary vascular pressure which results in perfusion of more of the vascular bed.

We conclude that none of these methods is accurate enough or simple enough to demonstrate an increase in lung water in patients. We propose that these approaches be abandoned and that direct measurements should be made of the permeability of the pulmonary epithelium or endothelium to different hydrophilic solutes.

## NEW METHODS FOR MEASURING THE PERMEABILITY OF PULMONARY VASCULAR ENDOTHELIUM AND ALVEOLAR EPITHELIUM

The methods available are:

(i) Measurement of rate of disappearance from air or fluid-filled alveoli of a number of hydrophilic tracer molecules of different molecular weight (endothelial plus epithelial permeability).

(ii) Measurement of rate of disappearance from blood of a similar range of tracers either into pulmonary lymph (endothelial permeability) or into fluid-filled alveoli (endothelial + epithelial permeability).

(iii) Indicator dilution curves (endothelial permeability) using a range of tracer molecules in a single pass through the vascular bed. It was concluded by Staub (1974) that, because of the large individual variability and lack of reproducibility in the indicator-dilution techniques, quite large changes must be necessary before one can be sure that a real difference from normal really exists.

Fluid-filled lobes of lungs have been utilized extensively in the measurement of alveolar epithelial permeability. The technique itself, by changing the normal air–liquid interface of the alveoli, may increase permeability; it also has very limited applicability to man.

This paper will conclude by reviewing a number of recent developments in the techniques for measuring pulmonary endothelial and epithelial permeability that may be applicable to studies in patients.

### *Measurement of solute flux across the pulmonary endothelium (large mol. wt. tracer)*

Gorin and his group (1978) using sheep, and Prichard, Rajagopalan and Lee (1980) using dogs, have measured the solute flux across the pulmonary vascular wall of these animals using non-invasive techniques which could be developed for use in man. Gorin and colleagues (1978) measured the flux of $^{113}$Indium-transferrin (mol. wt. 76 000 daltons) from the vascular compartment into the pulmonary interstitial space using external scintillation detectors, and pulmonary blood volume was measured using $^{99}$Tc-labelled red blood cells. A slightly different approach was developed by Prichard, Rajagopalan and Lee (1980), in which the flux of $^{125}$I-albumin from pulmonary capillary to lung interstitium was measured, again using external scintillation counting. The latter group measured the extracellular space volume rather than pulmonary blood volume using sodium $^{125}$iodide.

Gorin and colleagues (1978) showed a close correlation between the direct measurement in sheep of transvascular protein flux into pulmonary lymph and the indirect, non-invasive measurement of protein flux. They administered live *Pseudomonas aeruginosa* organisms to these animals and showed an increase in permeability by both methods. Prichard, Rajagopalan and Lee (1980) altered pulmonary hydrostatic or plasma osmotic pressure in dogs and showed a linear relationship between protein flux and ($\Delta P - \Delta\pi$), confirming that protein flux through the normally leaky endothelium is dependent on water flow (equation (3)). Following administration of either alloxan, pseudomonas organisms or after haemorrhagic hypotension, there was a much greater increase in protein flux.

Gorin, Kohler and De Nardo (1980) have modified the method for use in man. The major disadvantage for clinical use is the length of time, about 90 min, required to obtain the data. It might be difficult to obtain ideal conditions for external counting in sick patients for such a period. Nevertheless, these techniques provide an opportunity to measure, non-invasively, the flux of protein across the pulmonary capillary endothelium in man.

### *Measurement of solute flux across the pulmonary epithelium (small mol. wt. tracer)*

At about the time these studies appeared we were developing techniques with which the permeability of the alveolar epithelium could be examined in man, using equipment and radiolabelled tracers that were readily available in most hospitals. A major requirement was that the technique should be either non- or minimally-invasive and that the results should be immediately available at the conclusion of the test so that they could be of value in patient management. This excluded methods using tracer molecules labelled with β-emitting isotopes in which the preparation of samples for counting is very time-consuming and the equipment is available only in major medical centres. Our choice of γ-emitting tracers was dictated by the speed and ease of measurement and by the readily available γ-counting equipment routinely used in most hospitals.

The technique was based on the work of Chinard (1966) and Enna and Shanker (1972) who, extending observations made in the last century, showed that small volumes of tracer solutions injected into the airways and alveoli of animals and humans could be used to give an indication of alveolar epithelial permeability.

The development of the Northwick Park technique was in two parts, first in animals and then in humans.

### *Animal studies*

*Preliminary experiments.* Studies in animals (Berry et al., 1977; Jones et al., 1978, 1979) used a mixture of two tracer molecules injected as a 1–2 ml bolus into the airways. One of these tracers was the lipophilic molecule $^{125}$I-antipyrine (mol. wt. 312 daltons) which is freely diffusible through cell membranes. Because of its rapid rate of disappearance from the alveoli into blood ($T_{\frac{1}{2}}$ approx. 0.5 min) (Enna and Shanker, 1972), it is a good reference indicator of the perfusion of lung units in contact with the tracer mixture. The other tracer was the hydrophilic molecule $^{51}$Cr-ethylenediamine tetra-acetic acid (Cr-EDTA) (mol. wt. 377 daltons) which is very poorly diffusible across the normal pulmonary epithelium ($T_{\frac{1}{2}}$ approx. 200 min). We reasoned that an accelerated extraction from the lung of the hydrophilic molecule relative to the lipophilic molecule would indicate damage to the alveolar epithelium. This increase in permeability of the epithelium occurs either by an increase in number or size of equivalent pores in the intercellular junction or by shedding of the bilipid layer of the cell membrane.

Following intratracheal injection of the tracer mixture, sequential arterial blood samples were taken and the radioactivity of each sample was measured. Corrections were made for the different activities of each tracer in the injectate and curves were plotted of the counts of $^{125}$I-antipyrine and $^{51}$Cr-EDTA (fig. 7, left).

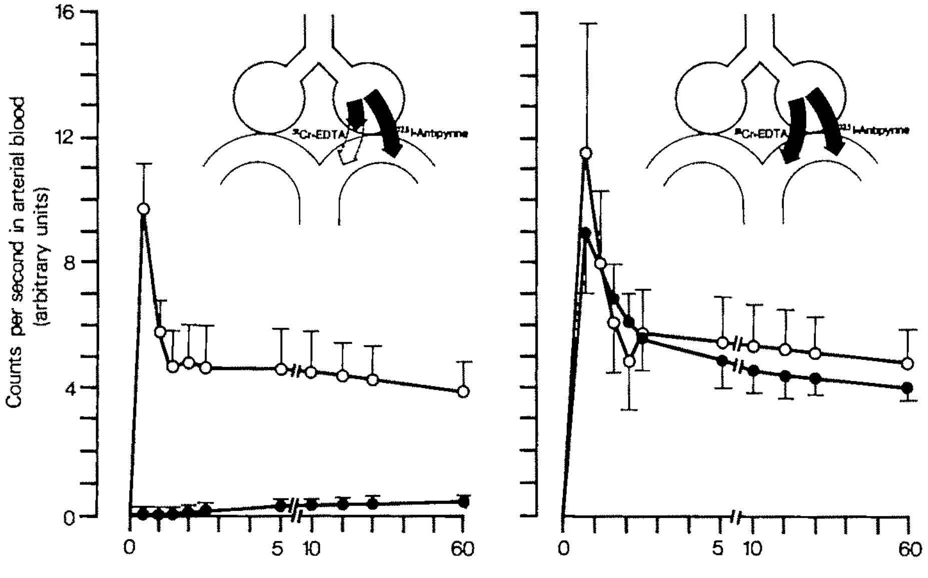

FIG. 7. Studies of alveolar epithelial permeability (left) before and (right) after aspiration into the lungs of hydrochloric acid 2 ml kg$^{-1}$ (pH 1). ○ = $^{125}$I-antipyrine (I-AP) and ● = $^{51}$Cr-EDTA. In both cases I-AP crosses rapidly from the alveoli into arterial blood. Before epithelial damage the $^{51}$Cr-EDTA crosses very slowly. After damage the rate of transport of $^{51}$Cr-EDTA and I-AP is virtually identical.

The index of permeability was expressed as the ratio of the area under the $^{51}$Cr-EDTA curve to that under the $^{125}$I-antipyrine ($^{125}$I-AP) curve during the first 5 min following tracheal injection. An index derived during this time interval minimizes errors resulting from different volumes of distribution in the body and the different clearance rates of the two tracers from the body. In normal animals the ratio $^{51}$Cr-EDTA/$^{125}$I-AP was 0.02, whereas following pulmonary aspiration of hydrochloric acid (pH 1) it was found that the $^{51}$Cr-EDTA crossed the alveolar epithelium as rapidly as did the $^{125}$I-AP (fig. 7, right) and the ratio $^{51}$Cr-EDTA/$^{125}$I-AP increased to 1.0, a more than 50-fold increase in permeability index. The effect of instilling graded concentrations of hydrochloric acid was to produce a graded effect on the lung permeability index from pH 1 to pH 3 but no demonstrable effect on lung permeability of dilutions of hydrochloric acid from pH 4 to pH 7.

Parallel studies of lung mechanics, gas exchange and chest radiography (Jones et al., 1979) showed that a persistent increase in permeability index was associated with large function changes attributable to the considerable increase in lung water.

This method can be used, with minor modification, in man and with this end in mind had been further developed by Huchon, Little and Murray (1981).

*Huchon's modification of the Northwick Park Technique.* These workers introduced their tracers as an aerosol, substituting $^{99}$Tc-diethylene triamine pentacetic acid ($^{99}$Tc-DTPA) for $^{51}$Cr-EDTA. $^{125}$I-AP was included in the aerosol to compute the quantity of Tc-DTPA delivered and $^{111}$In-DTPA was injected i.v. to calculate the quantity of Tc-DTPA passing from the lungs into the body tissues. They showed that the technique was capable of detecting an increase in alveolar epithelial permeability in a group of dogs following intrabronchial instillation of hydrochloric acid 1 ml kg$^{-1}$ (pH 1) and in another group following pulmonary fat embolism with oleic acid. In contrast, the permeability of the alveolar epithelium in dogs in which pulmonary oedema was induced by high left atrial pressure was not significantly different from controls.

The advantage of this approach is that it requires only a few venous blood samples, the aerosol can be delivered non-invasively and patients need not be lying still during the procedure. The requirement for three isotopes is a drawback: indium-111 may not be readily available for use in humans and iodine-125 has a long half-life so that the number of serial studies may have to be limited.

*Pulmonary epithelial permeability index using a single tracer.* A considerable simplification of this technique was suggested by Jones and his colleagues (1980) and Rinderknecht and his group (1980), based on the technique of Taplin and Chopra (1978). This technique was developed in man, but to complete this section on animal studies we will outline the method and mention its use to study the effect of oleic acid and neutral fat embolism on alveolar epithelial permeability (Jones et al., 1982).

In these experiments a small (<1 ml) bolus of $^{99}$Tc-DTPA was injected into the airways of anaesthetized prone rabbits as previously described (Jones et al., 1978). Two miniature collimated scintillation detectors were positioned over the lungs and head respectively and counts were made from the two fields at 1-min intervals. The counts obtained in the field of the head detector were used to correct for the increase in counts in blood and tissue in the field of the lung detector (described under human applications below). A monoexponential decay curve was derived which represented the rate of disappearance of $^{99}$Tc-DTPA from the alveoli into blood. In control animals the slope of this curve had a half-time ($T_{\frac{1}{2}}$) of approximately 200 min. The effect of i.v. injection of either saline, oleic acid or neutral fat is shown in figure 8. Within 1 min of injection of oleic acid there was an abrupt change in slope of the $^{99}$Tc-DTPA curve. This preceded changes in gas exchange or chest x-ray. No change was seen in the curves after injection of saline or neutral fat, neither was there any change in function or in chest radiograph in the latter two groups of animals. The curves obtained after oleic acid, however, could be resolved into two components, a first component where approximately 50% of the alveoli containing Tc-DTPA had $T_{\frac{1}{2}}$ approximately 3 min and a second component where $T_{\frac{1}{2}}$ was about 40 min. These animals subsequently developed severe abnormalities of gas exchange, lung mechanics and chest x-ray and a highly significant increase in lung water.

A dose–response curve is needed for i.v. oleic acid *v.* permeability index to establish the role of the technique in predicting the likelihood of lung damage. It remains to be seen whether a single tracer such as $^{99}$Tc-DTPA can fulfil this requirement or whether it is necessary to use a range of different molecular weight tracers similar in mass to those used by Matalon and Egan (1981).

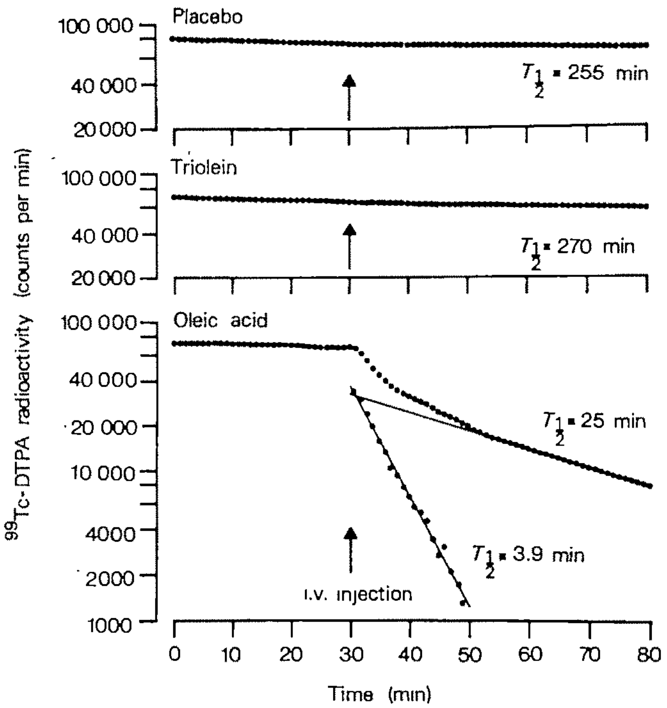

FIG. 8. The single tracer method for measuring alveolar epithelial permeability. Three groups of animals were studied. In each case the clearance of $^{99}$Tc-DTPA from lung to blood ($T\frac{1}{2}$ LB) was determined before and after i.v. injection of saline (placebo), triolein or oleic acid. Only the oleic acid group showed any change in permeability. (Reproduced by permission of the editor and publisher, *Thorax*.)

*Human studies*

We have extended our observations in animals to produce a single tracer technique for use in man. The basis of the method was to deliver the $^{99}$Tc-DTPA tracer into the lungs as an aerosol then measure the disappearance rate as it diffused through the alveolar and airway epithelium into the capillaries (Jones et al., 1980).

*Aerosol generation and delivery.* The major determinant of the deposition of an aerosol is the mass of the individual particles. Because many aerosols are water-based their particle density is assumed to be nearly 1 g ml$^{-1}$ and the mass of the particle is expressed in terms of the particle size. Three different forces operate within the airways to remove particles from the inhaled air: (i) *Inertial impaction.* This causes deposition at points of branching in large airways and is potentiated with increased particle size (> 5 μm) and air velocity, but is unimportant in small airways where linear velocity is low. (ii) *Sedimentation.* In the terminal air spaces of the lungs particles are removed by *sedimentation* which is proportional to particle size and the time available for settling. (iii) *Diffusion.* Particles smaller than 0.5 μm are deposited on the walls of the alveoli by molecular diffusion.

For a given aerosol the two most important parameters determing the deposition of particles are the mean diameter and distribution of particle diameters. Irregular particles are described by the "aerodynamic diameter" which is the diameter of a unit density sphere with the same settling velocity as the particle in question.

To measure the size distribution of aerosols of liquid particles we used a seven-stage Batelle type of cascade impactor in which the particles impact onto a series of seven circular glass cover slips, each of which collects particles of a known size distribution (I.A.E.A. 1978).

The aerosol of $^{99}$Tc-DTPA was generated using an Acorn nebulizer which produces particles up to 8 μm in diameter. The amount of radioactivity on each cover slip was summed and the cumulative percentage of this sum on each slip was plotted against particle size on a logarithmic-probability plot. From this plot the mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) were derived.

For our test of alveolar epithelial permeability, deposition was required to be maximum in the alveolar region and minimal in the tracheobronchial tree. These conditions are fulfilled with particles of diameter 0.5–2 μm (Chan and Lippman, 1980). The deposition and retention of particles in this size range are least affected by chronic cigarette smoking (Lourenço, Klimak and Borowski, 1971), chronic obstructive lung disease (Lourenço, Loddenkepmer and Carton, 1972) or pattern of ventilation (Task Group on Lung Dynamics, 1966).

In order to achieve a clinically useful mass of aerosol particles in the range 0.5–2 μm we modified the output of the Acorn nebulizer by passing the aerosol through a horizontal plate elutriator. This gave an MMAD of 0.9 μm with a GSD of 1.8.

*Derivation of an index of alveolar epithelial permeability in man.* $^{99}$Tc-DTPA (mol. wt. 492 daltons, approximate molecular radius 0.57 nm) is one of a family of labelled stable chelates that are chemically inert and electrically neutral. The half-life of this isotope (6 h) is very much shorter than chromium-51 used in our earlier animal studies. Initial experiments were carried out with the gamma camera to establish that the aerosol was evenly distributed over the lung fields. Supine subjects breathed the aerosol for a 3-min period. Tracheal deposition was not seen using the aerosol particle distribution described above (fig. 9).

Because of the high cost of the gamma camera it was decided to use cheaper and more readily available scintillation detectors positioned over the chest. To establish the dose of $^{99}$Tc-DTPA delivered to the lungs, an aerosol mixture of $^{99}$Tc-DTPA and $^{125}$I-antipyrine was breathed for 3 min. To standardize for the redistribution in body tissues of these two tracer molecules an i.v. infusion of $^{51}$Cr-EDTA and $^{125}$I-antipyrine was administered over the same 3-min period. Sequential samples of venous blood were taken and from these data were calculated the dose delivered and the clearance rate of $^{99}$Tc-DTPA from lung to blood ($T_{\frac{1}{2}\,\mathrm{LB}}$).

The $T_{\frac{1}{2}\,\mathrm{LB}}$ derived by this complex technique was compared with that obtained with the simple method outlined in the section on animal experiments. Again with the subject in the supine position, one detector was placed over the right upper chest and the other over the leg pointing away from the bladder. The $^{99}$Tc-DTPA aerosol was inhaled for 3 min then the breathing circuit and aerosol generator were removed from the vicinity of the detectors. Counts were taken every 1 min from both detectors until the radioactivity from the lung field had decreased to approximately 50% of the initial counts and these data were plotted on a semi-logarithmic graph *v.* time. A bolus of $^{99}$Tc-DTPA was then injected i.v. and counting was continued for a further 10–15 min. The purpose of this injection was to correct the counts from the lung field detector for radioactivity building up in the vascular tissues in the field of this counter. The i.v. isotope is distributed to the fields of both lung and leg counter and produced a step-wise increase in counts in the two regions (fig. 10). The counts in the lung field increase more rapidly than those in the leg field. Once a stable curve is achieved it is extrapolated backwards, the correction factor is derived and is used to subtract the appropriate fraction of the leg trace from the lung trace. The results were expressed as the half-time clearance from lung to blood ($T_{\frac{1}{2}\,\mathrm{LB}}$). These results compared closely to the $T_{\frac{1}{2}\,\mathrm{LB}}$ curves obtained with the multi-tracer technique described above (N. Veall, personal communication).

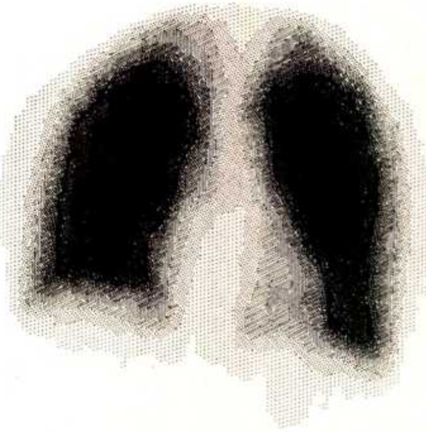

FIG. 9. The uniform distribution in the lungs of $^{99}$Tc-DTPA is shown after inhaling the aerosol for 3 min.

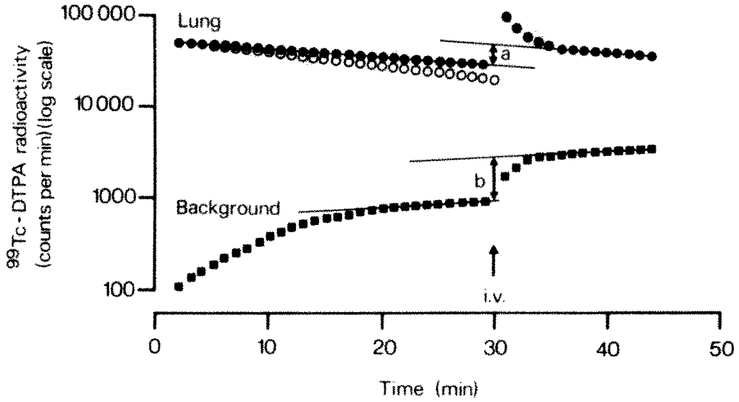

FIG. 10. The clearance of $^{99}$Tc-DTPA from the lung (●), accumulation in the leg (■) and the method of correcting for tissue background within the counting field of the lung detector. The curve corrected for tissue background is also shown (○). The time for this curve to fall by 50% is the $T_{\frac{1}{2}LB}$ value. ○ = ● − [(a/b) × ■].

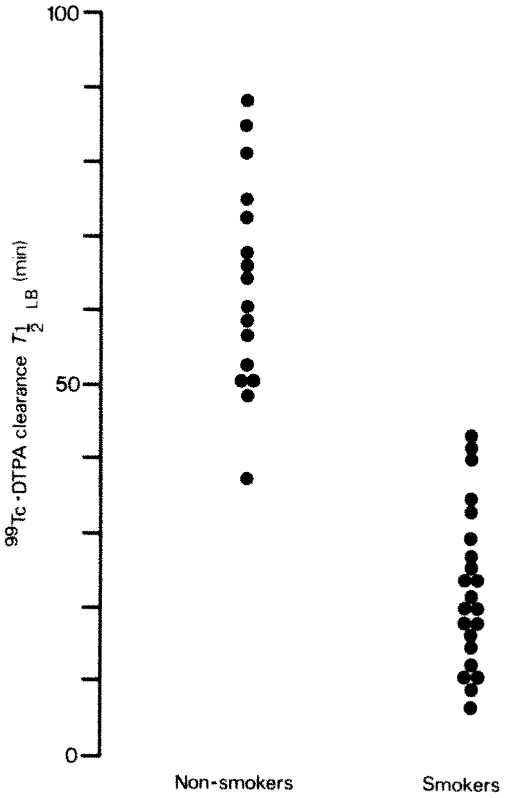

FIG. 11. $T_{\frac{1}{2}\,LB}$ values for non-smokers and symptomless cigarette smokers. Smokers have much leakier lungs (shorter $T_{\frac{1}{2}\,LB}$) than non-smokers.

*Results using this technique.* (i) *Normal subjects.* A mono-exponential clearance curve was found in all symptomless subjects. A significant difference in $T_{\frac{1}{2}\,LB}$ was found when non-smokers were compared with cigarette smokers (fig. 11). The mean $T_{\frac{1}{2}\,LB}$ in non-smokers was 59 ± 5 min (SEM) and in smokers it was 17 ± 3 min (SEM).

This increase in permeability in cigarette smokers is comparable to the findings in animals reported by Simani, Inoue and Hogg (1974). Using electron microscopy they showed that the electron-dense marker, horseradish peroxidase (mol. wt. 40 000 daltons) did not penetrate the pulmonary epithelium of normal animals, whereas animals exposed to cigarette smoke showed penetration of this marker through the epithelium into the interstitial space.

Following cessation of smoking there was recovery of the permeability defect so that even after 24 h there was a significant increase in $T_{\frac{1}{2}\,LB}$ compared with the smoking value. The recovery was proportional to the initial value (fig. 12) (Minty, Jordan and Jones, 1981).

*Results.* (ii) *Patients.* We are using this technique to study a group of non-smoking patients in the intensive care unit. Some of these have conditions which are known to predispose to the Adult Respiratory Distress Syndrome (ARDS). Examples of two of these are shown in figure 13. One patient (B) developed dyspnoea immediately following a laparotomy for severe intra-abdominal bleeding as a result of an ectopic pregnancy. The clearance curve

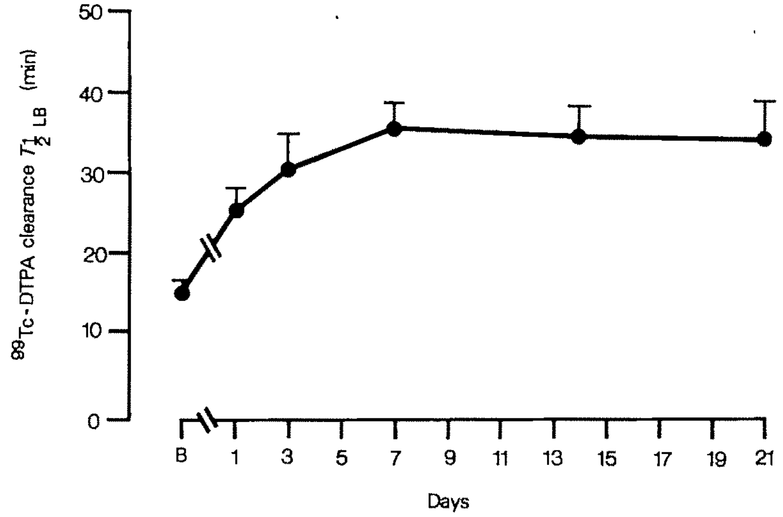

FIG. 12. Cessation of smoking leads to partial recovery of the permeability defect.

of $^{99}$Tc-DTPA measured at this time was resolved into two components similar to that seen following oleic acid embolism in rabbits, and showed a very rapid fast component and a slower, but still highly abnormal, second component. Plasma protein concentrations and pulmonary artery wedge pressures were normal. This is an example of severe damage to the alveolar epithelium. The patient was ventilated

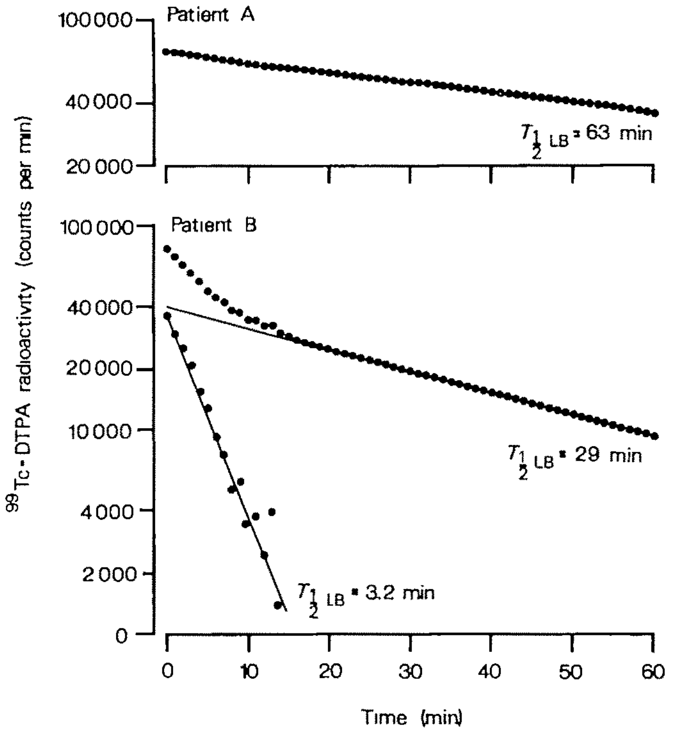

FIG. 13. Studies in two patients with pulmonary oedema show a normal $T_{\frac{1}{2}}$ LB in subject A with high pressure pulmonary oedema but a multi-exponential curve in subject B with leaky lungs.

and treated with steroids. The pulmonary microvascular pressures were reduced with diuretics and sodium nitroprusside. The patient made a rapid and full recovery. This recovery was associated with a return to a normal clearance for $^{99}$Tc-DTPA. We have used the technique in nine other patients with a similar predisposition to ARDS. In five of these the clearance of $^{99}$Tc-DTPA was highly abnormal and in two of these the curves were multi-exponential. These results initiated earlier and appropriate aggressive management. In one non-smoker with pulmonary oedema following a left-sided heart failure, the clearance rate of $^{99}$Tc-DTPA was normal (fig. 13, patient A). This difference between pulmonary oedema resulting from a permeability defect and that caused by left heart failure has been reported before (Uszler, Mason and Effros, 1981).

## CONCLUSION

We are now in a position to measure, with a minimally invasive test, an index of pulmonary epithelial permeability which is very sensitive to epithelial damage. It remains to be established how much $T_{\frac{1}{2}\,\mathrm{LB}}$ must decrease to indicate incipient pulmonary oedema. The lowest value of $T_{\frac{1}{2}\,\mathrm{LB}}$ that we have seen in symptomless smokers was 6 min and the $T_{\frac{1}{2}\,\mathrm{LB}}$ in the fast component of patients with shock lung was 2 ± 1 min. To improve the predictive power of the test for pulmonary oedema it is likely that a tracer with a larger molecular weight will be needed. In its present form, however, the test is already a considerable advance on pre-existing techniques.

## REFERENCES

Berry, M., Crawley, J. C. W., Hulands, G. H., Jones, J. G., and Minty, B. D. (1977). The influence of [H$^+$] on lung permeability to ($^{51}$Cr-EDTA). *J. Physiol. (Lond.)*, **267**, 32P.

Cander, L., and Forster, R. E. (1959). Determination of pulmonary parenchymal tissue volume and pulmonary capillary blood flow in man. *J. Appl. Physiol.*, **14**, 541.

Chait, A., Cohen, H. E., Meltzer, L. E., and Van Durme, J. P. (1972). The bedside chest radiograph in the evaluation of incipient heart failure. *Radiology*, **105**, 563.

Chan, T. L., and Lippmann, M. (1980). Experimental measurements and empirical modelling of the regional deposition of inhaled particles in humans. *Am. Ind. Hyg. Assoc. J.*, **41**, 399.

Chenoweth, D. E., Cooper, S. W., Hugli, T. E., Stewart, R. W., Blackstone, E, H., and Kirklin, J. W. (1981). Complement activation during cardiopulmonary by-pass. *N. Engl. J. Med.*, **304**, 497.

Chinard, F. P. (1966). The permeability characteristics of the pulmonary blood-gas barrier; in *Advances in Respiratory Physiology* (ed. C. G. Caro), p.106. Baltimore: Williams and Wilkins.

—— (1980). The alveolar-capillary barrier. Some data and speculations. *Microvasc. Res.*, **19**, 1.

Davies, M. (1973). Functions of biological membranes; in *Outline Studies in Biology*. London: Chapman and Hall.

Diana, J. N., and Fleming, B. P. (1979). Some current problems in microvascular research. *Microvasc. Res.*, **18**, 144.

Effros, R. M. (1978). Small solutes and water; in *Lung Water and Solute Exchange* (ed. N. C. Staub), p.183. New York: Marcel Dekker Inc.

Egan, E. A. (1980). Response of alveolar epithelial solute permeability to changes in lung inflation. *J. Appl. Physiol.*, **49**, 1032.

Enna, S. J., and Shanker, L. S. (1972). Absorption of drugs from the rat lung. *Am. J. Physiol.*, **223**, 1227.

Fein, A., Grossman, R. F., Jones, J. G., Goodman, P. C., and Murray, J. F. (1979a). Evaluation of transthoracic electrical impedence in the diagnosis of pulmonary edema. *Circulation*, **60**, 1156.

—— —— —— Overland, E., Pitts, L., Murray, J. F., and Staub, N. C. (1979b). The value of edema fluid protein measurement in patients with pulmonary edema. *Am. J. Med.*, **67**, 32.

Gorin, A. B., Kohler, J., and De Nardo, G. (1980). Non-invasive measurement of pulmonary transvascular protein flux in normal man. *J. Clin. Invest.*, **66**, 869.

—— Weidner, W. J., Demling, R. H., and Staub, N. C. (1978). Non-invasive measurement of pulmonary transvascular protein flux in sheep. *J. Appl. Physiol.*, **45**, 225.

Grossman, R. F., Jones, J. G., and Murray, J. F. (1980). Effects of oleic acid induced pulmonary edema on lung mechanics. *J. Appl. Physiol.*, **48**, 1045.

Guyton, A. C., and Lindsey, A. W. (1959). Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema. *Circ. Res.*, **7**, 649.

Hammerschmidt, D. E., Weaver, L. J., Hudson, L. D., Craddock, P. R., and Jacobs, H. S. (1980). Association of complement activation and elevated plasma C5a with adult respiratory distress syndrome. *Lancet*, **1**, 947.

Hollinger, M. A., Giri, S. N., Patwell, S., Zuckerman, J. E., Gorin, A., and Parsons, G. (1980). Effect of acute lung injury on angiotensin converting enzyme in serum, lung lavage and effusate. *Am. Rev. Respir. Dis.*, **121**, 373.

Huchon, G. J., Little, J. W., and Murray, J. F. (1981). Assessment of alveolar-capillary membrane permeability of dogs by aerosolization. *J. Appl. Physiol.*, **51**, 955.

I.A.E.A. (1978). Particle size analysis in estimating the significance of airborne contamination. *Technical Reports Series 179*, **71**.

Inoue, S., Michel., R. P., and Hogg, J. C. (1976). Zonulae occludentes in alveolar epithelium and capillary endothelium of dog lungs studied with the freeze–fracture technique. *J. Ultrastruct. Res.*, **56**, 215.

Jones, J. G., Berry, M., Hulands, G. H., and Crawley, J. C. (1978). The time course and degree of change in alveolar capillary membrane permeability induced by aspiration of hydrochloric acid and hypotonic saline. *Am. Rev. Respir. Dis.*, **118**, 1007.

—— Grossman, R. F., Berry, M., Slavin, G., Hulands, G. H., and Minty, B. (1979). Alveolar-capillary membrane permeability. Correlation with functional, radiographic and post mortem changes after fluid aspiration. *Am. Rev. Respir. Dis.*, **120**, 399.

—— Lemen, R., and Graf, P. D. (1978). Changes in airway calibre following pulmonary venous congestion. *Br. J. Anaesth.*, **50**, 735.

—— Milledge, J. S. (1980). The respiratory mass spectrometer;

in *Current Developments in the Clinical Applications of HPLC, GC and MS. C.R.C. Symposium* No. 1, 167.

Jones, J. G., Minty, B. D., Beeley, J. M., Royston, D., Crow, J., and Grossman, R. F. (1982). Pulmonary epithelial permeability is immediately increased after embolisation with oleic acid but not with neutral fat. *Thorax*, 37, 169.

—— —— Lawler, P., Hulands, G., Crawley, J. C. W., and Veall, N. (1980). Increased alveolar epithelial permeability in cigarette smokers. *Lancet*, 1, 66.

Lewis, F. R., and Elings, V. I. (1978). Microprocessor determination of lung water using thermal-green dye double indicator dilution. *Surg. Forum*, 29, 182.

Lourenço, R. V., Klimak, M. J., and Borowski, C. J. (1971). Deposition and clearance of 2 μ particles in the tracheobronchial tree of normal subjects—smokers and non-smokers. *J. Clin. Invest.*, 50, 1411.

—— Loddenkemper, R., and Carton, R. W. (1972). Patterns of distribution and clearance of aerosols in patients with bronchiectasis. *Am. Rev. Respir. Dis.*, 106, 857.

Matalon, S., and Egan, E. A. (1981). Effects of 100% $O_2$ breathing on permeability of alveolar epithelium to solute. *J. Appl. Physiol.*, 50, 859.

Minty, B. D., Jordan, C., and Jones, J. G. (1981). Rapid improvement in abnormal pulmonary epithelial permeability after stopping cigarettes. *Br. Med. J.*, 282, 1183.

Prichard, J. S., Rajagopalan, B., and Lee, G. de J. (1980). Transvascular albumin flux and the interstitial water volume in experimental pulmonary oedema in dogs. *Clin. Sci.*, 59, 105.

Rinderknecht, J., Shapiro, L., Krauthammer, M., Taplin, G., Wasserman, K., Uszler, J. M., and Effros, R. M. (1980). Accelerated clearance of small solutes from the lungs in interstitial lung disease. *Am. Rev. Respir. Dis.*, 121, 105.

Said, S. I. (1979). *Metabolic and Endocrine Functions of the Lung. Current Concepts*. Kalamazoo: Upjohn Company.

Schneeberger, E. E., and Karnovsky, M. J. (1976). Substructure of intercellular junctions in freeze-fractured alveolar-capillary membranes of mouse lung. *Circ. Res.*, 38, 404.

Severinghaus, J. W., Catron, C., and Noble, W. (1972). A focusing electrode bridge for unilateral lung edema. *J. Appl. Physiol.*, 32, 526.

Simani, A. S., Inoue, S., and Hogg, J. C. (1974). Penetration of the respiratory epithelium of guinea pigs following exposure to cigarette smoke. *Lab. Invest.*, 31, 75.

Snashall, P. D. (1980). Pulmonary oedema. *Br. J. Dis. Chest*, 74, 2.

Staehelin, L. A., and Hull, B. E. (1978). Junctions between living cells. *Sci. Am.*, 238, 140.

Starling, E. H. (1896). On the absorption of fluids from the connective tissue spaces. *J. Physiol. (Lond.)*, 19, 312.

Staub, N. C. (1974). Pulmonary edema. *Physiol. Rev.*, 54, 678.

—— (1978). Pulmonary edema due to increased microvascular permeability to fluid and protein. *Circ. Res.*, 43, 143.

—— (1981). Pulmonary edema due to increased microvascular permeability. *Ann. Rev. Med.*, 32, 291.

Taplin, G. V., and Chopra, S. K. (1978). Inhalation lung imaging with radioactive aerosols and gases. *Prog. Nucl. Med.*, 46, 619.

Task Group on Lung Dynamics (1966). Deposition and retention models for internal dosimetry of the human respiratory tract. *Health Phys.*, 12, 173.

Taylor, A. E., and Gaar, K. A. (1970). Estimation of equivalent pore radii of pulmonary capillary and alveolar membranes. *Am. J. Physiol.*, 218, 1133.

—— Guyton, A. C., and Bishop, V. S. (1965). Permeability of the alveolar membrane to solutes. *Circ. Res.*, 16, 353.

Uszler, J. M., Mason, G., and Effros, R. M. (1981). Determination between hemodynamic and nonhemodynamic pulmonary edema by inhaled soluble radioaerosol. *J. Nucl. Med.*, 22, 43.

*Br. J. Anaesth.* (1982), **54**, 723

# ADULT RESPIRATORY DISTRESS SYNDROME

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The Adult Respiratory Distress Syndrome (ARDS) refers to the clinical expression of severe injury to the gas exchanging units of the lung: the alveoli and their associated capillary beds. It is characterized by marked parenchymal pulmonary inflammation and increased permeability of the alveolar capillary unit resulting in severe hypoxaemia and widespread infiltrates on chest x-ray (Ashbaugh et al., 1967; Petty and Ashbaugh, 1971).

Adult respiratory distress syndrome is not a single disease, but rather a final common pathway for many insults which may injure the lung directly or indirectly (table I). Its importance is reflected by the estimated 150 000 cases seen in the United States in 1976 (Lung Program, 1972). Our own recent experience indicates that ARDS constitutes approximately 5% of all critical care admissions, with systemic sepsis accounting for 50%, trauma 15%, cardiopulmonary bypass 15%, viral pneumonia 10% and drug ingestion 5% of cases. Mortality is high in the syndrome, ranging from 20% (Douglas and Downs, 1977) to 83% (Lee et al., 1981), probably reflecting the diversity of lung injuries and patient populations reported.

The clinical presentation of the ARDS has been described as progressing through four phases (Gomez, 1968). Phase one is characterized by profound dyspnoea and tachypnoea with a normal chest x-ray. In phase two, or the latent period, increasing cyanosis and hypoxaemia are associated with minor chest x-ray abnormalities. Respiratory failure, with profound hypoxaemia, reduced compliance, and diffuse bilateral infiltrates, superevenes in phase three. Finally, hypoxaemia becomes unresponsive to oxygen, and metabolic and respiratory acidosis develop. It must be emphasized however, that a given patient may present in any of these stages. Progression may or may not occur, depending on the nature and severity of the insult, treatment and host response.

TABLE I. *Conditions associated with ARDS*

| Presumed direct injury | Presumed indirect injury |
|---|---|
| Thoracic trauma—Contusion | Systemic sepsis |
| Aspiration | Shock of any cause |
| Gastric juice | Non-thoracic trauma |
| Drowning | Drugs |
| Hydrocarbon | Heroin, methadone |
| Inhaled toxins | Aspirin, barbituates |
| Smoke | Ethchlorvynol |
| Corrosive chemicals | Blood transfusions |
| Infection | Pancreatitis |
| Viral, bacterial | Severe neurological injury |
| Miliary TB | |
| Legionella | Post-cardiopulmonary bypass |
| Emboli | |
| Amniotic fluid embolus | Diabetic ketoacidosis |
| Fat emboli | |
| Lymphangiogram | |
| Radiation | |

## PATHOLOGY

It is generally accepted that injury to the alveolar units results in similar pathophysiological consequences regardless of whether the insult is delivered by inhalation or carried by the blood stream. As stated by Bachofen and Weibel (1977) "... the pattern of cell damage and repair is lung specific rather than specific for the damaging factor..."

The normal alveolus (figs 1 and 2) provides an extensive surface area for gas exchange. The alveolar space is surrounded by an epithelial layer beneath which a vast capillary bed is supported by a fine connective tissue network (fig. 1). The alveolar wall measures 2 μm in thickness, but is only 0.5 μm at its thinnest part where most of the gas exchange takes place (fig. 2). Approximately 95% of the alveolar surface is covered by Type I epithelial cells and the remainder by Type II granular epithelial cells. Type I cells do not divide and are believed to be derived from Type II cells which are metabolically active and synthesize surfactant (Bachofen and Weibel, 1977). The alveolar epithelium and its associated

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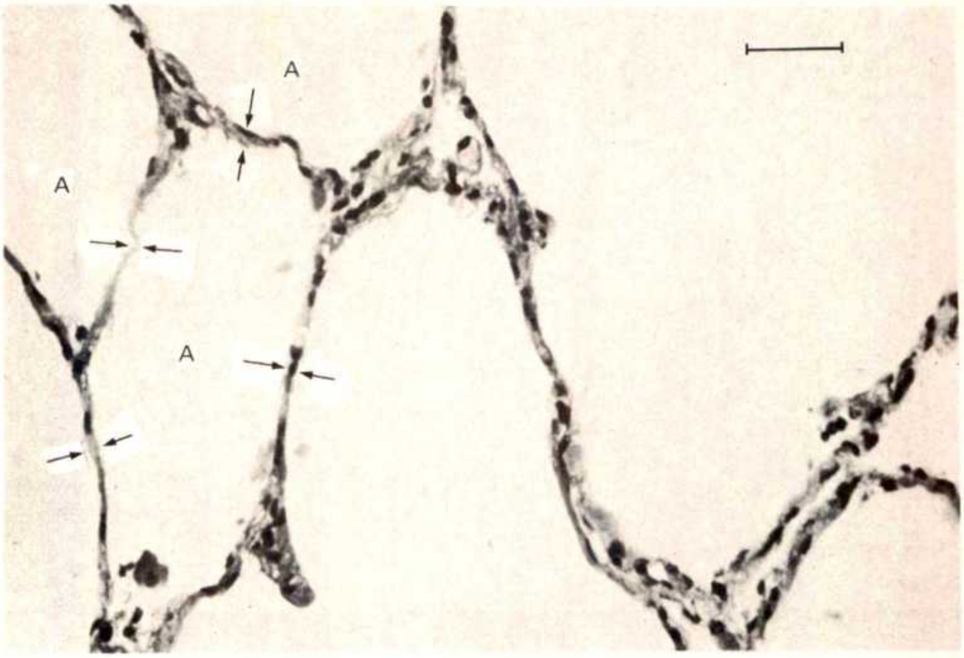

FIG. 1. Normal human lung. Pulmonary capillaries lie in thin septae. A = alveolar space; → ← = alveolar septum. Horizontal bar represents 0.1 mm.

capillary will be henceforth called the alveolar capillary membrane.

The pulmonary response to acute injury and subsequent repair can be studied in three stages: first an early exudative phase (24–96 h), and a subsequent proliferative phase (3–10 days) in which a florid cellular reaction is followed finally by a diffuse fibrotic reaction beginning 7–10 days after the initial injury (Orell, 1971; Katzenstein, Bloor and Liebow, 1976; Bachofen and Weibel, 1977; Pratt et al., 1979; Connors, McCaffree and Rogers, 1981).

The early exudative phase (figs 3 and 4) is characterized by oedema, capillary congestion, and infiltration of the interstitium by erythrocytes and leucocytes (Orell, 1971; Bachofen and Weibel, 1977). The Type I alveolar lining cell is more susceptible to injury than the resistant Type II cell and shows variable degrees of degeneration. Marked necrosis is noted primarily over the thinnest portion of the alveolar capillary membrane where most of the gas exchange takes place. The capillary endothelial cell remains relatively normal, even in areas subjacent to severe epithelial cell destruction. Surprisingly, there are no visible endothelial gaps which could account for passage of protein-rich oedema fluid, erythrocytes and leucocytes from the vascular to the interstitial and alveolar spaces. Hyaline membranes are conspicuous in areas of severe epithelial damage and are most prominent in the respiratory bronchioles and alveolar ducts (Orell, 1971; Pratt et al., 1979). Microthrombi and capillary plugging by leucocytes which are frequently observed bear no relationship to the extent of the injury (Bachofen and Weibel, 1977).

In the proliferative phase (fig. 5) dividing Type II pneumocytes completely cover the alveolar septum in some area. Denuded basement membranes are rare and alveolar oedema is less widespread. As the syndrome progresses there is thickening of the epithelium by proliferating Type II cells, enlargement of the interstitium by oedema, leucocytes, fibroblasts and fibres, and a decrease in the number of capillaries (Bachofen and Weibel, 1977).

The fibrotic phase (fig. 6) is characterized by the deposition of fibrous tissue in the alveolar septae and hyaline membranes and can progress to diffuse involvement of the entire lung. Hyaline membranes become infiltrated with fibroblasts and are transformed into fibrous tissue. Alveolar duct fibrosis is a characteristic feature of patients who die after pro-

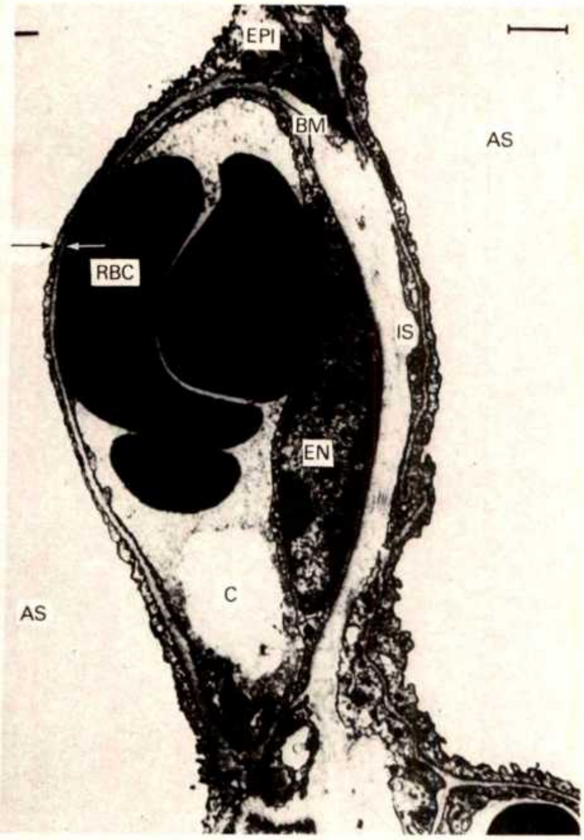

FIG. 2. Normal alveolar septum. The alveolar capillary membrane is composed of capillary endothelium, epithelium and interstitial space. Note thin portion (arrows) where fused basement membranes separate endothelium from epithelium and most of the gas exchange takes place. AS = alveolar space, EPI = Type I epithelial cell, BM = basement membrane, EN = endothelial cell, C = capillary. Horizontal bar represents 1 μm.

longed respiratory distress (Orell, 1971; Pratt et al., 1979). It has been observed that the severity of pathological change does not correlate with the duration of the illness and it is speculated that high concentrations of inspired oxygen may contribute to hyaline membrane formation and alveolar duct fibrosis (Pratt et al., 1979).

## PHYSIOLOGICAL CONSEQUENCES

ARDS is characterized by reduced lung volumes, reduced compliance (increased lung stiffness) and severe hypoxaemia (Pontoppidan, Geffen and Lowenstein, 1972). These alterations in the mechanical and gas exchanging properties result directly from injury to the alveolar epithelium and pulmonary capillary bed.

### *Reduced lung volume*

There are several mechanisms by which lung volume is reduced. These include: (1) fluid-filled alveoli which occupy a smaller volume and do not participate in ventilation, (2) alveolar collapse consequent to abnormal surfactant function, (3) reduced ventilation to alveolar units as a result of small airway compression by interstitial oedema fluid, and (4) increased surface tension which decreases compliance and results in smaller lung volume at any given transpulmonary pressure. The abnormalities in surfactant function may be consequent to decreased production, the synthesis of an abnormal product or inactivation of surfactant by oedema fluid (Connors, McCaffree and Rogers, 1981). Despite the proliferation of metabolically active Type II cells, normal surface active material may not be synthesized by them.

### *Reduced compliance*

Another feature of ARDS is reduced lung compliance, manifested clinically by the high airway pressures necessary to deliver an adequate tidal volume. The mechanisms include increased surface tension and loss of lung volume as a result of atelectasis and oedema fluid (Nobel, Kay and Obdrzalek, 1975; Ryan et al., 1978). In experimental models (Cook et al., 1959; Johnson et al., 1964; Nobel, Kay and Odbrzalek, 1975; Ryan et al., 1978) interstitial oedema and vascular congestion have been shown to have little or no effect on lung compliance. The development of diffuse parenchymal fibrosis further reduces lung compliance and makes the alveolus more difficult to distend and ventilate (Lamy et al., 1976).

### *Gas exchange*

The profound hypoxaemia which characterizes ARDS appears to be caused by shunts and perfusion of lung regions with extremely low ventilation–perfusion ($\dot{V}/\dot{Q}$) ratios (Dantzker et al., 1979). Shunting results from alveolar collapse and flooding with oedema fluid. The creation of low $\dot{V}/\dot{Q}$ regions may result from compression of small airways by interstitial oedema with a reduction of ventilation to distal alveolar units. Alternatively, there may be some fluid-filled alveoli the volume of which increases sufficiently at the end of inspiration

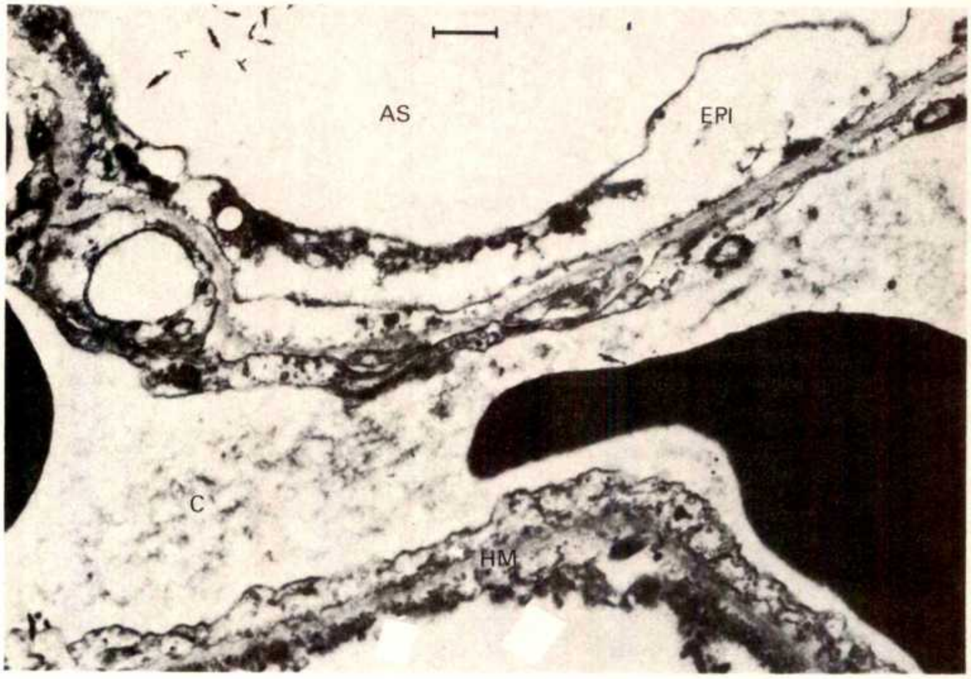

FIG. 3. Early ARDS. Swelling of Type I epithelial cell cytoplasmic extension (EPI) overlying thin portion of alveolar capillary membrane. Note hyaline membrane (HM) lining alveolar wall. AS = alveolar space, C = capillary. Horizontal bar represents 1 $\mu$m.

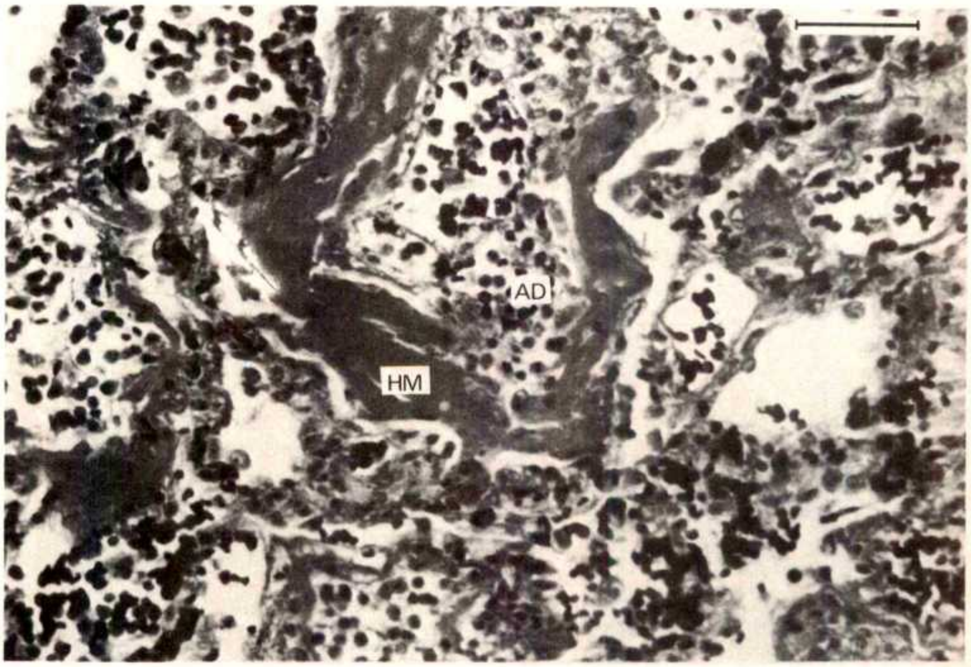

FIG. 4. Exudative phase, ARDS. Inflammatory interstitial and alveolar exudate. Hyaline membrane lines alveolar duct. AD = alveolar duct, HM = hyaline membrane. Horizontal bars represents 0.05 mm.

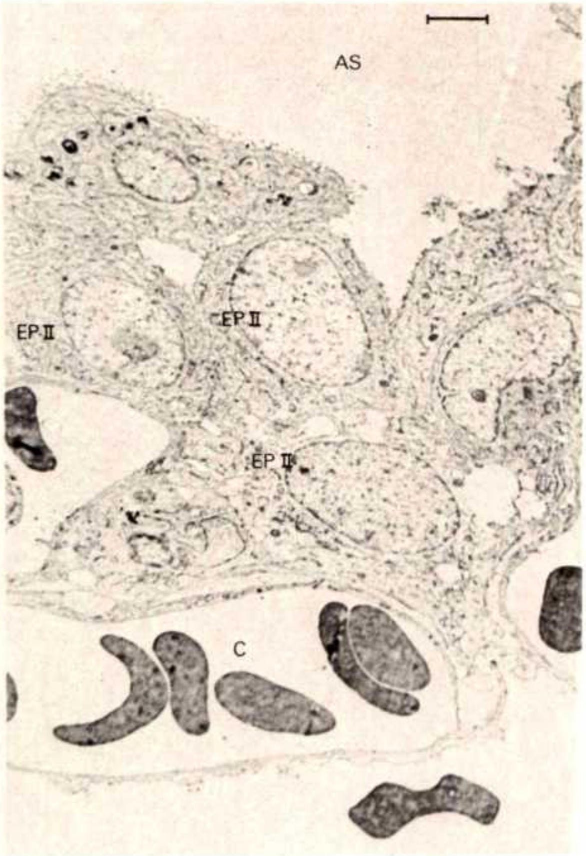

FIG. 5. Proliferative phase, ARDS. Marked increase in Type II epithelial cells which bulge into alveolar space. EPII = Type II alveolar epithelial cell, C = capillary, AS = alveolar space. Horizontal bar represents 1 μm.

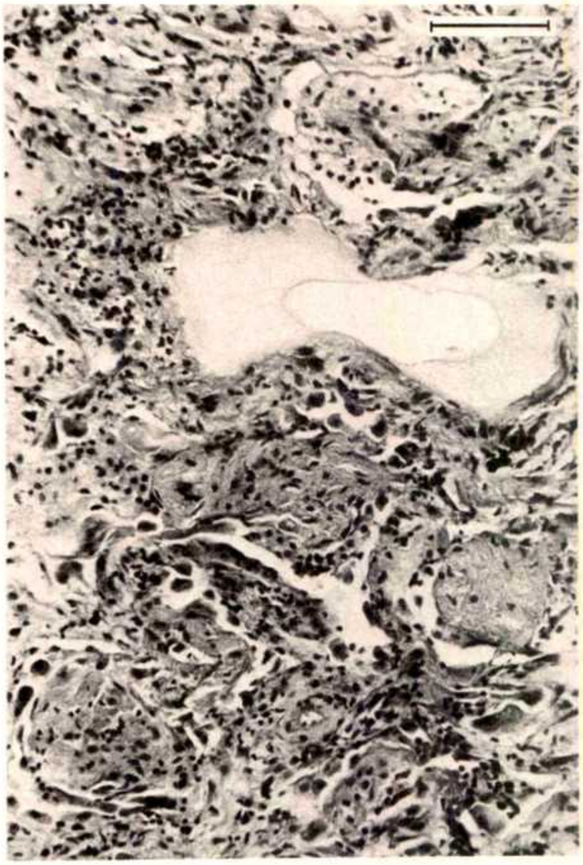

FIG. 6. Fibrotic phase, ARDS. Organization of alveolar exudates with almost complete obliteration of alveolar spaces. The alveolar septae are thickened by an infiltration of fibroblasts and fibrous tissue. Horizontal bar represents 0.1 mm.

to permit some gas transfer, especially at high inspired oxygen concentrations.

Using the multiple insert gas method, Dantzker and his colleagues (1979) defined a bimodal distribution of ventilation–perfusion ratios in ARDS. The upper mode consisted of units with a normal $\dot{V}/\dot{Q}$ which received 52% of the cardiac output. The lower mode receiving the remainder of the cardiac output consisted of either pure shunt or shunt plus a small region with very low $\dot{V}/\dot{Q}$ ratios. These abnormal distributions account for all the observed hypoxaemia, making reduced diffusion an unlikely mechanism in this setting.

Lamy and colleagues (1976) made pathophysiological correlations in 45 patients with severe ARDS and defined three distinct groups. The first demonstrated a fixed shunt with no improvement in $Pa_{O_2}$ when the inspired oxygen concentration ($FI_{O_2}$) was increased or when positive end expiratory pressure (PEEP) was added. Open lung biopsy showed extensive consolidation by interstitial and alveolar oedema, exudates and haemorrhage. A second group showed improvement in $Pa_{O_2}$ with increasing $FI_{O_2}$ and PEEP, but the response occurred slowly over several hours. Lung biopsies revealed marked fibrosis with organization of alveolar exudates. A third group with less severe hypoxaemia had no fibrosis and less extensive oedema than the first group. $Pa_{O_2}$ improved with increasing $FI_{O_2}$ and a prompt and dramatic response to PEEP was observed.

Early in the course of the illness carbon dioxide elimination is normal. As the disease progresses there is obliteration of pulmonary capillary beds

(Bachofen and Weibel, 1977) creating lung regions with high $\dot{V}/\dot{Q}$ resulting in increased physiological deadspace (Pontoppidan, Geffen and Lowenstein, 1972; Dantzker et al., 1979). This can lead to impaired carbon dioxide elimination and an increase in $Pa_{CO_2}$ if minute ventilation does not increase (Hopewell and Murray, 1976).

## PATHOPHYSIOLOGY

Adult Respiratory Distress Syndrome may be understood as the disruption of normal fluid and solute filtration in the lung resulting from diffuse pulmonary inflammation. Under normal conditions, fluid filtration is governed by the Starling equation (Starling, 1896) (fig. 7) which states that filtration across the endothelium into the interstitial spaces is the resultant of hydrostatic and protein osmotic pressure gradients. Several mechanisms act to prevent pulmonary oedema under normal clinical conditions (Staub, Nagano and Pearce, 1967). Pulmonary lymphatics actively pump fluid out of the interstitium in the early stages of pulmonary oedema. Without adequate lymphatic function alveolar flooding will develop even when there is normal integrity of the alveolar capillary membrane (Cowan, Staub and Edmunds, 1976). Alveolar Type I cells are joined by tight junctions which are almost completely im-

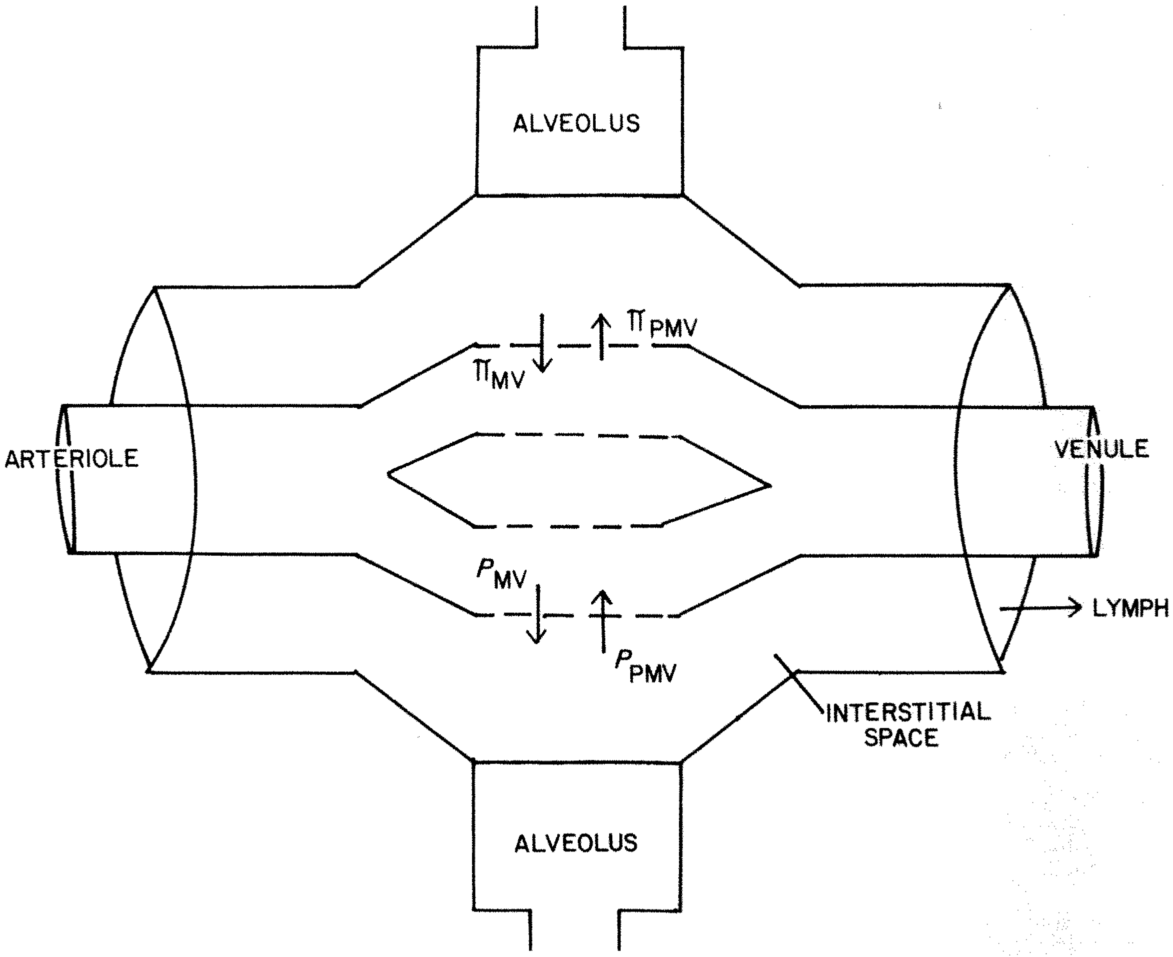

FIG. 7. The Starling equation states that $\dot{Q} = K[(P_{MV} - P_{PMV}) - \sigma(\pi_{MV} - \pi_{PMV})]$ where $\dot{Q}$ = fluid flux, $K$ = apparent filtration coefficient, $P_{MV}$ = perimicrovascular hydrostatic pressure, $\sigma$ = apparent reflection coefficient, $\pi_{MV}$ = microvascular colloid osmotic pressure and $\pi_{PMV}$ = perimicrovascular colloid osmotic pressure. This equation indicates that fluid filtration across the endothelium of the lung is determined by the balance between hydrostatic and osmotic pressure gradients.

permeable to water, solutes and protein, thereby limiting their access to the alveoli (Schneeberger-Keeley and Karnovsky, 1968; Goetzman and Vissher, 1969). In addition to these mechanisms, any increase in the microvascular hydrostatic pressures will dilute interstitial proteins thereby lowering protein osmotic pressure and reducing the outflow gradient. It has been estimated that half of the increase in microvascular pressure may be offset by this mechanism (Erdmann et al., 1975; Staub, 1980).

Pulmonary oedema may develop when there is a significant alteration of any aspect of the Starling equation. However, most important clinically are those changes leading to an increased permeability as occurs in ARDS, or high pressure as occurs in left ventricular failure. Permeability pulmonary oedema (ARDS) has been characterized as rapid in onset, producing a protein-rich oedema fluid as a result of injury to the alveolar capillary membrane. Driving pressures as reflected by the pulmonary capillary wedge pressure are normal or low (Vreim and Staub, 1976; Fein et al., 1979). Greatest attention has recently been focused on the role of (1) disordered neutrophil kinetics (Lee et al., 1981; Morgan et al., 1981), (2) complement activation (Craddock, Fehr et al., 1977; Craddock, Hammerschmidt et al., 1977; Hammerschmidt et al., 1980) and (3) haemostasis in the generation of indirect lung injury (Saldeen, 1976; Belew et al., 1978). Although all of these mechanisms may be important, it is most reasonable to view them as an interacting feedback system leading to ARDS. These will now be reviewed.

Our own work has recently demonstrated that the acute phases of ARDS are associated with neutrophilic alveolitis (Lee et al., 1981; Morgan et al., 1981). Events gleaned by observations in haemodialysis and cardiopulmonary bypass indicate that activation of complement C5a produces sequestration of neutrophils in the microvasculature of the lung (Craddock, Fehr et al., 1977; Craddock, Hammerschmidt et al., 1977; Chenoweth et al., 1981). Clinically, activated complement has been found in patients who are septic (Hammerschmidt et al., 1980) or have undergone cardiopulmonary bypass (Chenoweth et al., 1981). Such neutrophils, when stimulated, elaborate three classes of inflammatory mediators (Weissmann, Smolen and Korchak, 1980): proteolytic enzymes, arachidonic acid metabolites and oxygen-free radicals. Only the first has been definitely associated with clinical ARDS.

Elastase, although initially absent from the bronchoalveolar lavage of patients with ARDS (Fowler, Gidas and Hyers, 1981), is found in increased concentration within the first 48 h (Lee et al., 1981). These proteases can injure the pulmonary microvasculature directly (Cochrane and Aikin, 1966; Janoff, 1970) and generate activated complement (Henson et al., 1979; Olsson and Venge, 1980) and elastin fragments (Morgan et al., 1981) which are chemotactic for monocytes and macrophages (Senior, Griffen and Mecham, 1980). Neutrophil-derived arachidonic acid metabolites have diverse effects depending on the molecule released (Kitchen, Boot and Dawson, 1978). However, members of the PGE series potentiate the inflammatory response and are weakly chemotactic for neutrophils (Farel-Hutchinson et al., 1980). Oxygen-free radicals produced by neutrophils are highly reactive. They damage the structure of the alveolar capillary membrane (McCord and Fridovich, 1978; Sacks et al., 1978) and inactivate alpha-1-protease inhibitor (Carp and Janoff, 1979; Abrams et al., 1980) the most important local defence against protease injury.

A role for disordered coagulation in the generation of ARDS has been suggested by the presence of platelet and fibrin microemboli in the lung (Saldeen, 1976), and pulmonary platelet accumulation during the acute phases of ARDS (Schneider, Zapol and Carvalho, 1980). In addition to obstructing the pulmonary vascular bed, platelets synthesize and release a variety of vasoactive peptides and proteases, including histamine, bradykinin and elastase (Mustard and Packham, 1979). Sustained permeability changes have not, however, been demonstrated following platelet embolization in animals (Binder et al., 1980).

A role for deficient or damaged surfactant in the generation of ARDS is supported by several pieces of circumstantial evidence. First there is similarity between the half-life of surfactant and the "latent" period between lung injury and clinical manifestations of ARDS. This suggests that alveolar Type II cells, damaged early in ARDS, are no longer producing surfactant, or that surfactant is being inactivated. Second, loss of free and intracellular surfactant in experimental lung injury is correlated with acute alveolar injury and reduced compliance (Ryan et al., 1981). Finally, surfactant recovered from humans with ARDS is abnormal structurally and functionally (Petty et al., 1977). Thus, disturbed surfactant production and function may contribute to the manifestations of ARDS.

## MANAGEMENT OF ARDS

### *Mechanical ventilation*

The primary treatment objectives in ARDS are improvement of arterial blood oxygen tension and tissue oxygen delivery without precipitating pulmonary oxygen toxicity. All patients are treated initially with supplementary oxygen by mask or nasal prongs. In patients in whom hypoxaemia becomes progressively worse, it becomes necessary to initiate mechanical ventilation. This decision is based on general patient status, rate of deterioration, and nature of injury. In general, mechanical ventilation is begun when hypoxaemia ($Pa_{O_2} < 8$ kPa, 60 mm Hg) persists in the face of potentially toxic concentrations of oxygen ($FI_{O_2} > 0.70$) (Clark and Lambertsen, 1971). Volume-cycle respirators are used in order to deliver adequate tidal volumes in patients with "stiff" lungs. Large tidal volumes ($10-15 \text{ ml kg}^{-1}$) are used as a means to prevent progressive atelectasis and improve blood oxygenation (Sykes, Young and Robinson, 1965; Visick, Fairley and Hickey, 1973).

Two frequently encountered problems in patients breathing spontaneously who are being ventilated are asynchronous breathing and hyperventilation. The former may be corrected by increasing the respiratory rate or inspiratory flow. Intermittent mandatory ventilation (IMV) may be of benefit in either situation because the patient is allowed to breathe spontaneously in-between ventilator breaths, thereby reducing minute ventilation and correcting the respiratory alkalosis. Furthermore, the use of IMV may reduce the need for sedation or paralysis.

### *Positive end expiratory pressure (PEEP)*

PEEP has an established role in ARDS management. Its beneficial effects result from an increase in lung volume with consequent improvement in $Pa_{O_2}$ and compliance (Nicotra et al., 1964; Kumar et al., 1970; Falke, Pontoppidan and Kumar, 1972; Pontoppidan, Geffen and Lowenstein, 1972; Sugarman, Rogers and Miller, 1972; Gong and Tierney, 1980). This permits a reduction in $FI_{O_2}$ from potentially toxic values. In the oedematous condition, the increase in lung volume results in a redistribution of alveolar fluid with a reduction in the distance for oxygen diffusion (Staub, 1974). PEEP has not been shown to decrease extravascular lung water (Staub, 1974; Hopewell, 1979).

Alternatively, it has recently been demonstrated that a decrease in cardiac output by itself can reduce shunt in patients with ARDS (Lemaire et al., 1978; Dantzker, Lynch and Weg, 1980). The effect of PEEP on cardiac output is unpredictable, but it is known that a decrease in output may result (see below). In such a circumstance, the improvement in $Pa_{O_2}$ may result from reduced perfusion to the diseased areas of the lung in the absence of improvement in lung function. Therefore, oxygen delivery may be reduced following PEEP even when $Pa_{O_2}$ is increased (Dantzker et al., 1980).

Several reports suggest that PEEP would prevent ARDS from developing in high-risk patients (Schmidt et al., 1978; Weigelt, Mitchell and Snyder, 1979) but this is not well substantiated (Hudson, 1981).

### *Systemic oxygen transport*

Although mechanical ventilation and PEEP usually improve $Pa_{O_2}$, a decrease in haemoglobin concentration or cardiac output can result in a decrease in the amount of oxygen delivered to the tissues. Tissue oxygen delivery (systemic oxygen transport) is the product of cardiac output and arterial oxygen content ($Ca_{O_2}$). $Ca_{O_2}$ is a function of $Pa_{O_2}$, the haemoglobin concentration and saturation. We recommend $Pa_{O_2}$ between 8 and 9.3 kPa (60–70 mm Hg) and a haemoglobin concentration of $10 \text{ g dl}^{-1}$ (by transfusion, if necessary) in order to maintain an adequate $Ca_{O_2}$. The tissue delivery of oxygen under such conditions would then depend on the cardiac output.

Several years ago Suter, Fairley and Isenberg (1975) proposed that maximal delivery of oxygen (and cardiac output) could be correlated with the highest respiratory system compliance in patients treated with PEEP. More recent evidence questions the validity of these earlier observations (Hudson et al., 1977; Hudson, 1981), and we feel that reliable and accurate cardiac output assessment requires direct measurement.

### *Steroids*

The use of corticosteroids in ARDS is a controversial and confused issue. Substantial evidence of clinical efficacy is lacking. These hormones are known to stabilize lysosomal membranes (Wilson, 1972), prevent complement-induced neutrophil aggregation (Hammerschmidt et al., 1977), and superoxide damage to endothelial cells *in vitro* (Sacks et al., 1978). In animal systems, pretreatment with steroids prevents the increased lung vascular permeability following endotoxic shock (Brigham, Bowers and McKeen, 1981) and may improve survival of rats exposed to pure oxygen (Sahebjami, Gawd and Massaro, 1974).

Shumer (1976) demonstrated improved survival using steroids in a study of patients with septic shock. Sibbald and colleagues (1981) found alveolar capillary integrity to be maintained as measured by $^{131}$I-albumin clearance. Other studies suggest possible benefits in radiation pneumonitis (Castellano et al., 1974) and fat embolism (Fisher et al., 1971) treated with corticosteroids, but these were not controlled studies.

Currently, despite the controversy, we use corticosteroids in the treatment of septic ARDS. Benefits in other forms of this syndrome are even less well-defined. At the present time, despite the potential role of prostaglandins and fibrinogen in the pathogenesis of ARDS, there are no animal or human trials suggesting a clinical role for manipulating these substances.

## MONITORING

### *Ventilators*

Ventilator monitoring is used in conjunction with clinical examination, chest x-ray and arterial blood-gas measurement in defining resolution or progression of illness. The monitoring of respiratory system mechanics (lung and chest wall) in patients on respirators has recently been reviewed (Bone, 1976; 1981). These techniques include measuring effective (dynamic) and static compliance of the respiratory system. The tidal volume divided by the peak end inspiratory airway pressure is the effective (dynamic) compliance. The same tidal volume divided by the plateau pressure, recorded when the patient relaxes against a momentary occlusion of the expiratory tubing, is the static compliance. The effective (dynamic) compliance reflects the elastic- and flow-resistive components of the system, while the static compliance measures only the elastic properties. The combined use of these two measurements may permit the early identification of complications. For example, reduced effective (dynamic) compliance without a change in the static measurement can occur in bronchoconstriction or increased airway narrowing as a result of retained secretions. A reduction in both compliance measurements can be seen in tension pneumothorax, atelectasis, bronchial intubation, worsening parenchymal consolidation and oedema (Bone, 1976).

These compliance characteristics are frequently the first indication of complicating pulmonary disease and improvement of these measurements follows the institution of appropriate therapy (Bone, 1976).

### *Haemodynamic*

Pulmonary artery balloon-tipped catheters (Swan et al., 1970) permit the measurement of pulmonary capillary wedge pressure (PCWP), which estimates left arterial pressure, cardiac output by thermodilution and mixed venous oxygen tension—a reflection of tissue oxygenation. The indications for catheterization include: uncertainty about the presence of left ventricular failure, refractory hypotension, suspected low intravascular volume and an anticipated use of high levels of PEEP.

In general, haemodynamic monitoring guides the physician in dealing with two major clinical dilemmas. First, the patient who presents with acute dyspnoea, hypoxaemia and diffuse infiltrates on chest x-ray may have either cardiac or permeability pulmonary oedema. As the distinction is difficult on clinical grounds alone (Dershaw et al., 1981), measurement of the PCWP permits the separation of these two entities. Second, there is the problem of appropriate fluid management. A low wedge pressure would support the need for fluid repletion; a high pressure, the need for restriction and diuresis. In many instances the physician must balance the risks of hypovolaemia and consequent reduced cardiac and urine output against the use of a higher wedge pressure which will increase extravascular lung water. Although PCWP 15–18 mm Hg has been recommended as a optimal left ventricular filling pressure following myocardial infarction (Crexels,. Chatterjee and Forrester, 1973), this would be inappropriate where there is increased alveolar capillary permeability. We recommend a pressure of 5–10 mm Hg, provided cardiac output can be maintained. The type of fluid, either crystalloid or colloid, is probably less important than the volume administered (Stothert and Carrico, 1981). Colloid offers no particular advantage since the osmotic gradient between the interstitial and vascular spaces is reduced because of the increased membrane permeability to protein.

In addition, the use of the pulmonary artery balloon catheter permits calculation of cardiac output either directly by thermodilution or indirectly by measurement of the mixed venous oxygen tension or saturation. Recent evidence suggests that the thermodilution method is to be preferred since the mixed venous oxygen tension may not accurately reflect decreases in cardiac output and tissue oxygenation in the critically ill (Getz et al., 1979; Danek et al., 1980; Hudson, 1981).

## COMPLICATIONS

There are several problems which frequently arise in the ventilatory management of patients with ARDS. These include: a paradoxical decrease in $Pa_{O_2}$, a reduction in cardiac output and barotrauma.

The application of PEEP to lungs where there is localized disease may have adverse effects on $Pa_{O_2}$. In such a circumstance, the positive pressure is preferentially transmitted to the normal more compliant lung units, thereby overdistending these alveoli. This can cause compression of pulmonary capillaries, leading to a redistribution of blood flow away from normal to diseased areas. The end result is a decrease in the arterial oxygen tension.

Several conditions could account for the reduction in cardiac output in patients treated with PEEP. These include a reduction in venous return or preload (Cournand et al., 1948; Lenfant and Howell, 1960; Lutch and Murray, 1972; Asbaugh and Petty, 1973; Qvist et al., 1975), an increase in pulmonary vascular resistance (Powers, Manual and Neclerio, 1973; Hobelmann et al., 1975) and impairment of myocardial performance (Cassidy et al., 1978; Sharf, Caldini and Ingram, 1977). A recent study (Calvin, Driedger and Sibbald, 1981) concluded that, in ARDS patients treated with PEEP up to 15 cm $H_2O$, a reduced left ventricular preload secondary to increased peripheral venous capacitance seemed responsible for the reduced cardiac output. This observation stresses the importance of haemodynamic monitoring for fluid management. In some patients, however, direct myocardial dysfunction may occur consequent to PEEP. Several mechanisms for this depression of myocardial function have been proposed and include changes in left ventricular geometry as a result of right ventricular overload (Jardin et al., 1981), neurogenic influences (Glick, Wechsler and Epstein, 1969) and a hormonal agent released from distended lungs (Manny, Patten and Liebman, 1978; Patten et al., 1978).

The risk of barotrauma is associated with the use of high tidal volumes and PEEP (Steir et al., 1974; Bone, Francis and Pierce, 1975; Hudson, 1981). Once maximal recruitment of alveoli occurs, a further increase in tidal volume could produce overdistension of alveolar volume. This is reflected in a decrease in compliance measurements (Bone, 1976), which should alert the clinician to the risk of pneumothorax.

## EXTRACORPOREAL MEMBRANE OXYGENATION

The development of membrane artificial lungs for the treatment of acute respiratory failure was stimulated by the belief that maintenance of gas exchange would sustain life while the lung healed (Zapol and Snider, 1980). A study designed to evaluate the efficacy of this therapy has shown that extrapulmonary oxygenation did not increase survival in patients with severe ARDS when compared with more conventional therapy (Zapol et al., 1979). The majority of patients died with progressive deterioration in respiratory function in the presence of diffuse inflammation, necrosis and fibrosis (Pratt et al., 1979).

Despite the disappointing results, considerable interest remains for continuing research in this area. As a result of the previous experience efforts are being directed toward improving the technology of blood oxygenators as well as investigating the body's physiological response to the procedure (Hempel and Lenfant, 1981). It appears at this time that extracorporeal membrane oxygenation remains an investigational technique.

## SUMMARY: PRINCIPLES OF MANAGEMENT

In summary, therapy of ARDS is directed at improving gas exchange and maintaining adequate fluid balance. There is no established therapy which will prevent the syndrome in high-risk patients or accelerate resolution and promote healing in cases of established disease. We attempt to improve gas exchange by mechanical ventilation and PEEP, and assure proper fluid balance by haemodynamic monitoring. An arterial $P_{O_2}$ of 8–9.3 kPa (60–70 mm Hg) is sufficient to provide adequate tissue oxygenation provided the cardiac output is normal and the haemoglobin concentration is at least 10 g $dl^{-1}$. If inspired oxygen tensions of 60% or greater are necessary, then PEEP should be applied in order to decrease $FI_{O_2}$.

## PULMONARY FUNCTION FOLLOWING ARDS

The mortality in ARDS is extremely high. Death results from either progressive respiratory failure (Lamy et al., 1976) or associated multi-system disease (Morgan et al., 1981). Among survivors, reports of sequelae are limited to small numbers of patients (Klein et al., 1976; Lakshminarayan, Stanford and Petty, 1976; Rotman et al., 1977; Yernault,

TABLE II. *Sequelae of ARDS*

| | % Abnormal |
|---|---|
| Clinical symptoms | 25 |
| Chest x-ray abnormalities | 20 |
| Hypoxaemia at rest | 13 |
| Hypoxaemia with exercise | 30 |
| Pulmonary function tests | |
| Restrictive | 34 |
| Obstructive | 22 |
| Airway hyper-reactivity | 24 |
| Reduced diffusing capacity for carbon monoxide ($D_L$CO) | 40 |

Englert and Sergysels, 1977; Simpson et al., 1978; Yahav, Lieberman and Molho, 1978; Gregory, Morris and Cengiz, 1981). Although they suggest that residual abnormalities in survivors improve with time, the cases studied tend to reflect a younger population with a predominantly infectious aetiology for ARDS.

A summary of these published reports is presented in table II. Prominent problems after recovery include dyspnoea, wheezing, recurrent infection and, rarely, upper airway obstruction. Physiological studies show marked impairment in 30–40% of survivors with airway hyper-reactivity occasionally developing. The factors that result in permanent lung damage are as yet unknown, but may relate to the nature and severity of the insult, oxygen concentrations used in therapy, age and underlying pulmonary dysfunction.

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### REFERENCES

Abrams, W. R., Eliraz, A., Kimbel, P., and Weinbaum, G. (1980). The effect of the oxidizing agents chloramine-T and cigarette smoke on dog serum proteinase inhibitor(s). *Exp. Lung Res.*, **1**, 211.

Ashbaugh, D. G., Bigelow, D. B., Petty, T. L., and Levine, B. E. (1967). Acute respiratory disease in adults. *Lancet*, **2**, 313.

—— Petty, T. L. (1973). Positive and expiratory pressure. Physiology, indications and contraindications. *J. Thorac. Cardiovasc. Surg.*, **65**, 165.

Bachofen, M., and Weibel, E. R. (1977). Alterations of the gas exchange apparatus in adult respiratory insufficiency associated with septicaemia. *Am. Rev. Respir. Dis.*, **116**, 589.

Belew, M., Gerdin, B., Parath, J., and Saldeen, T. (1978). Isolation of vasoactive peptides from human fibrin and fibrinogen degraded by plasmin. *Thromb. Res.*, **13**, 983.

Binder, A. S., Kageler, W., Perel, A., Flick, M., and Staub, N. (1980). Effect of platelet depletion on lung vascular permeability after microemboli in sheep. *J. Appl. Physiol.*, **48**, 414.

Bone, R. C. (1976). Diagnoses of causes for acute respiratory distress by pressure–volume curves. *Chest*, **70**, 740.

—— (1981). Monitoring respiratory function in the patient with adult respiratory distress syndrome. *Sem. Respir. Med.*, **2**, 140.

—— Francis, P. B., and Pierce, A. K. (1975). Pulmonary barotrauma complicating end-expiratory pressure. *Am. Rev. Respir. Dis.*, **111**, 921.

Brigham, K., Bowers, R. E., and McKeen, C. R. (1981). Methyl prednisone prevention of increased lung vascular permeability following endotoxemia in sheep. *J. Clin. Invest.*, **67**, 1103.

Calvin, J. E., Driedger, A. A., and Sibbald, W. J. (1981). Positive end expiratory pressure (PEEP) does not depress left ventricular function in patients with pulmonary edema. *Am. Rev. Respir. Dis.*, **124**, 121.

Carp, H., and Janoff, A. (1979). *In vitro* suppression of suppression of serum elastase-inhibitory capacity by phagocytosis polymorphonuclear leukocytes. *J. Clin. Invest.*, **64**, 793.

Cassidy, S. S., Robertson, C. H., Pierce, A. K., and Johnson, R. L. (1978). Cardiovascular effects of positive end-expiratory pressure in dogs. *J. Appl. Physiol.*, **44**, 743.

Castellano, R. A., Glatstan, E., Turbow, M. M., Rosenberg, S., and Kaplan, H. S. (1974). Latent radiation injury of lungs or heart activated by steroid withdrawal. *Ann. Int. Med.*, **80**, 593.

Chenoweth, D. E., Cooper, S. W., Hugli, T. E., Stewart, R. W., Blackstone, E. H., and Kirklin, J. W. (1981). Complement activation during cardiopulmonary bypass. Evidence for generation of C3a and C5a anaphylotoxins. *N. Engl. J. Med.*, **304**, 497.

Clark, J. M., and Lambertsen, C. J. (1971). Pulmonary oxygen toxicity: A review. *Pharmacol. Rev.*, **23**, 37.

Cochrane, C. G., and Aikin, B. S. (1966). Polymorphonuclear leukocytes in immunologic reactions. Destruction of vascular basement membrance *in vivo* and *in vitro*. *J. Exp. Med.*, **124**, 733.

Connors, A. F. jr, McCaffree, D. R., and Rogers, R. M. (1981). The adult respiratory distress syndrome; in *Disease-a-Month*, Vol. 27. Chicago, Ill.: Year Book Medical Publishers, Inc.

Cook, C. D., Mead, J., Schreiner, G. L., Frank, N. R., and Craig, M. J. (1959). Pulmonary mechanics during induced pulmonary edema in anesthetized dogs. *J. Appl. Physiol.*, **14**, 177.

Cournand, A., Mottley, H. L., Werko, L., and Richards, D. W. (1948). Physiologic studies of the effects of intermittant positive breathing on cardiac output in man. *Am. J. Physiol.*, **152**, 162.

Cowan, G. S. M., Staub, N. C., and Edmunds, L. H. (1976). Changes in the fluid compartments and dry weights of reimplanted dog lungs. *J. Appl. Physiol.*, **40**, 962.

Craddock, P. R., Fehr, J., Brigham, K. L., Kronenberg, R. S., and Jacob, H. S. (1977). Complement and leukocyte-mediated pulmonary dysfunction in hemodialysis. *N. Engl. J. Med.*, **296**, 769.

—— Hammerschmidt, D., White, J. G., Dalmasso, A. P., and Jacob, H. S. (1977). Complement (C5a)-induced granulocyte aggregation *in vitro*. A possible mechanism of complement-mediated leukostasis and leukopenia. *J. Clin. Invest.*, **60**, 260.

Crexels, C., Chatterjee, K., and Forrester, J. S. (1973). Optimal level of filling pressure in the left side of the heart in acute myocardial infarction. *N. Engl. J. Med.*, **289**, 1263.

Danek, S. J., Lynch, J. P., Weg, J. G., and Dantzker, D. R. (1980). The dependence of oxygen uptake on oxygen delivery in the adult respiratory distress syndrome. *Am. Rev. Respir. Dis.*, **122**, 387.

Dantzker, D. R., Brook, C. J., Dehart, P., Lynch, J. P., and

Weg, J. G. (1979). Ventilation–perfusion distributions in adult respiratory distress syndrome. *Am. Rev. Respir. Dis.*, **120**, 1039.

—— Lynch, J. P., and Weg, J. G. (1980). Depression of cardiac output as the mechanism of shunt reduction in the therapy of acute respiratory failure. *Chest*, **77**, 636.

Dershaw, B., Morgan, L., Goldberg, A., Lippmann, M., and Fein, A. (1981). The impact of pulmonary artery catheterization on diagnosis of the critically ill. *Crit. Care Med.*, **9**, 203.

Douglas, M. E., and Downs, J. B. (1977). Pulmonary function following severe acute respiratory failure and high levels of positive end-expiratory pressure. *Chest*, **71**, 18.

Erdmann, A. J. III, Vaughan, T. R., Brigham, K. L., Woolverton, W. C., and Staub, N. C. (1975). Effect of increased vascular pressure on lung fluid balance in unanesthetized sheep. *Circ. Res.*, **37**, 271.

Falke, K. J., Pontoppidan, H., and Kumar, A. (1972). Ventilation with end expiratory pressure in acute lung disease. *J. Clin. Invest.*, **51**, 2315.

Farel-Hutchinson, A. W.; Bray, M. A., Doig, M. V., Shipley, M. E., and Smith, M. J. H. (1980). Leukotriene B, a potent chemokinetic and aggreating substance released from polymorphonuclear leukocytes. *Nature (Lond.)*, **286**, 264.

Fein, A., Grossman, R. F., Jones, J. G., Overland, E., Pitts, L., Murray, J. F., and Staub, N. C. (1979). The value of edema fluid protein measurement in patients with pulmonary edema. *Am. J. Med.*, **67**, 32.

Fisher, J. E., Turner, R. H., Herndon, H. J., and Riseborough, E. J. (1971). Massive steroid therapy in severe fat embolism. *Surg. Gynecol. Obstet.*, **132**, 667.

Fowler, A. A., Gidas, P. C., and Hyers, Y. M. (1981). Protein and cell content of bronchoalveolar lavage fluid with adult respiratory distress syndrome. *Am. Rev. Respir. Dis.*, **423**, 247.

Getz, L. G., Weaver, L. J., Haisch, C. E., Kohler, T. R., Carrico, C. J., and Hudson, L. D. (1979). The relationship of mixed venous oxygen saturation to cardiac output during the initiation of PEEP in patients with ARDS. *Am. Rev. Respir. Dis.*, **119**, 117.

Glick, G., Wechsler, A. S., and Epstein, W. E. (1969). Reflex cardiovascular depression produced by stimulation of pulmonary stretch receptors in the dog. *J. Clin. Invest.*, **48**, 467.

Goetzman, B. W., and Vissher, M. B. (1969). The effects of alloxan and histamine on the permeability of the pulmonary alveolar-capillary barrier to albumin. *J. Physiol. (Lond.)*, **204**, 51.

Gomez, A. C. (1968). Pulmonary insufficiency in nonthoracic trauma. *J. Trauma*, **8**, 656.

Gong, H., and Tierney, D. F. (1980). Respiratory distress syndrome: Use of positive end-expiratory pressure and outcome; in *Current Pulmonology*, Vol. 2 (ed. D. H. Simmons), p. 103. Boston: Houghton Mifflin Professional Publishers.

Gregory, C. G., Morris, A., and Cengiz, M. (1981). Pulmonary function and exercise gas exchange in survivors of adult respiratory distress syndrome. *Am. Rev. Respir. Dis.*, **123**, 492.

Hammerschmidt, D. E., Weaver, L. J., Hudson, L. D., Craddock, P. R., and Jacob, H. S. (1980). Association of complement activation and elevated plasma-C5a with adult respiratory distress syndrome. Patho-physiological relevance and possible prognostic value. *Lancet*, **1**, 947.

—— White, J. G., Craddock, P. R., and Jacob, H. S. (1977). Corticosteroids inhibit complement-induced granulocyte aggregation. A possible mechanism for their efficacy in shock states. *J. Clin. Invest.*, **63**, 798.

Hempel, F. G., and Lenfant, C. J. M. (1981). Current and future research in adult respiratory distress syndrome. *Sem. Resp. Med.*, **2**, 165.

Henson, P. M., McCarthy, K., Larsen, G. L., Webster, R. O., Giclas, P. C., Dreisen, R. B., King, T. E., and Shaw, J. O. (1979). Complement fragments, alveolar macrophages, and alveolitis. *Am. J. Pathol.*, **97**, 93.

Hobelmann, C. F., Smith, D. E., Virgilio, R. W., Shapiro, A. R., and Peters, R. M. (1975). Hemodynamic alterations with positive end-expiratory pressure: The contribution of the pulmonary vasculature. *J. Trauma*, **15**, 951.

Hopewell, P. C. (1979). Failure of positive end-expiratory pressure to decrease lung water content in alloxan-induced pulmonary edema. *Am. Rev. Respir. Dis.*, **120**, 813.

—— Murray, J. F. (1976). The adult respiratory distress syndrome. *Ann. Rev. Med.*, **27**, 343.

Hudson, L. D. (1981). Ventilatory management of patients with adult respiratory distress syndrome. *Sem. Resp. Med.*, **2**, 128.

—— Tooker, J. Haisch, C. E., and Carrico, C. J. (1977). Does compliance reflect optimal oxygen transport with positive end-expiratory pressure? *Chest*, **67**, 156.

Janoff, A. (1970). Mediators of tissue damage leukocyte lysosomes. Further studies on granulocyte elastase. *Lab. Invest.*, **22**, 228.

Jardin, F., Fariot, J.-C., Boisante, L., Curien, N., Margairaz, A., and Bourdarias, J.-P. (1981). Influence of positive end-expiratory pressure on left ventricular performance. *N. Engl. J. Med.*, **304**, 387.

Johnson, J. W. C., Permutt, S. Sipple, J. H., and Salem, E. S. (1964). Effect of intra-alveolar fluid on pulmonary surface tension properties. *J. Appl. Physiol.*, **19**, 769.

Katzenstein, A. A., Bloor, C. M., and Liebow, A. A. (1976). Diffuse alveolar damage—the role of oxygen shock and related factors. *Am. J. Pathol.*, **85**, 210.

Kitchen, E. A., Boots, J. R., and Dawson, W. (1978). Chemotactic activity of thromboxan B2, prostaglandins and their metabolites for polymorphonuclear leucocytes. *Prostaglandins*, **16**, 239.

Klein, J. J., van Haeringen, J. R., Sluiter, H. J., Holloway, R., and Peset, R. (1976). Pulmonary function after recovery from the adult respiratory distress syndrome. *Chest*, **69**, 350.

Kumar, A., Falke, K. J., Geffin, B., Aldredge, C. F., Laver, M. B., Lowenstein, E., and Pontoppidan, H. (1970). Continuous positive-pressure ventilation in acute respiratory failure: Effects on hemodynamics and lung function. *N. Engl. J. Med.*, **283**, 1430.

Lakshminarayan, S., Stanford, R. E., and Petty, T. L. (1976). Prognosis after recovery from adult respiratory distress syndrome. *Am. Rev. Respir. Dis.*, **113**, 7.

Lamy, M., Fallat, R. J., Koeniger, E., Dietrich, H.-J., Ratlitt, J. L., Eberhart, E. C., Tucker, H. J., and Hill, J. D. (1976). Pathologic features and mechanisms of hypoxemia in adult respiratory distress syndrome. *Am. Rev. Respir. Dis.*, **114**, 267.

Lee, C. T., Fein, A. M., Lippmann, M., Holtzman, H., Kimbel, P., and Weinbaum, G. (1981). Elastolytic activity in pulmonary lavage fluid from patients with adult respiratory-distress syndrome. *N. Engl. J. Med.*, **304**, 192.

Lemaire, F., Gastine, F., Regnier, B., Teisseire, B., and Rapin, M. (1978). Perfusion changes modify intrapulmonary shunting ($Q_s/Q_t$) in patients with adult respiratory distress syndrome (ARDS). *Am. Rev. Respir. Dis.* (Suppl. 1) **117**, 144.

Lenfant, C., and Howell, B. J. (1960). Cardiovascular adjustments in dogs during continuous pressure breathing. *J. Appl.*

*Physiol.*, **15**, 425.

Lung Program (1972). National Heart and Lung Institute Respiratory Disease: Task force on problems, research approaches, needs. DHEW publ. No. (NIH)73-432, p. 172.

Lutch, J. S., and Murray, J. F. (1972). Continuous positive pressure ventilation: Effects of systemic oxygen transport and tissue oxygenation. *Am. Int. Med.*, **76**, 193.

McCord, J. M., and Fridovich, I. (1978). The biology and pathology of oxygen radicals. *Ann. Int. Med.*, **89**, 122.

Manny, J., Patten, M. T., and Liebman, P. R. (1978). The association of lung distention, PEEP, and biventricular failure. *Ann. Surg.*, **187**, 151.

Morgan, L. Kucich, U., Dershaw, B., Lippmann, M., Rosenbloom, J., Weinbaum, G., and Fein, A. (1981). Elastin degradation in the adult respiratory distress syndrome. *Am. Rev. Respir. Dis.*, **123**, 93.

Mustard, J. F., and Packham, M. A. (1979). The reaction of blood to injury; in *Inflammation, Immunity and Hypersensitivity* (ed. H. Z. Movat). Harper and Row.

Nicotra, M. B., Stevens, P. M., Viroslav, J., and Alvarez, A. A. (1964). Physiologic evaluation of positive end expiratory pressure. *Chest*, **64**, 10.

Nobel, W. H., Kay, J. C., and Obdrzalek, J. (1975). Lung mechanics in hypervolemic pulmonary edema. *J. Appl. Physiol.*, **38**, 681.

Olsson, I., and Venge, P. (1980). The role of the human neutrophil in the inflammatory reaction. *Allergy*, **35**, 1.

Orell, S. R. (1971). Lung pathology in respiratory distress following shock in the adult. *Acta Pathol. Microbiol. Scand.*, **79**, 65.

Patten, M. T., Liebman, P. R., Manny, J., Shepro, D., and Hechtman, H. B. (1978). Humorally-mediated alterations in cardiac performance as a consequence of positive end expiratory pressure. *Surgery*, **84**, 201.

Petty, T. L., and Ashbaugh, D. G. (1971). The adult respiratory distress syndrome: Clinical features, factors influencing prognosis and principles of management. *Chest*, **60**, 233.

—— Reiss, O. K., Paul, G. W., Silvers, G. W., and Elkins, N. D. (1977). Characteristics of pulmonary surfactant in adult respiratory disease syndrome associated with trauma and shock. *Am. Rev. Respir. Dis.*, **115**, 531.

Pontoppidan, H., Geffen, B., and Lowenstein, E. (1972). Acute respiratory failure in the adult. *N. Engl. J. Med.*, **287**, pp. 690, 743, 799.

Powers, S. R. jr, Manual, R., and Neclerio, M. (1973). Physiologic consequences of positive end expiratory pressure (PEEP) ventilation. *Ann. Surg.*, **178**, 265.

Pratt, P. C., Vollmer, R. T., Shellburne, J. D., and Crapo, J. D. (1979). Pulmonary morphology in a multihospital collaborative extracorporeal membrane oxygenation project. I. Light microscopy. *Am. J. Pathol.*, **95**, 191.

Qvist, J., Pontoppidan, H., Wilson, R. S., Lowenstein, E., and Laver, M. B. (1975). Hemodynamic responses to mechanical ventilation with PEEP: The effect of hypervolemia. *Anesthesiology*, **42**, 45.

Rotman, H. H., Lavelle, T. F. jr, Dimcheff, D. F., Van Den Belt, R. J., and Weg, J. G. (1977). Long-term physiologic consequences of the adult respiratory distress syndrome. *Chest*, **72**, 190.

Ryan, S. F., Barrett, C. R., Lavietes, M. H., Bell, A. L. L., and Rochester, D. F. (1978). Volume–pressure and morphometric observations after acute alveolar injury in the dog from N-nitro-N-methylurethane. *Am. Rev. Respir. Dis.*, **118**, 735.

—— Liau, D. F., Bell, A. L. L., Hashim, S. A., and Barrett, C. R. (1981). Correlation of lung compliance and quantities of surfactant phospholipids after acute alveolar injury from N-nitroso-N-methylurethane in the dog. *Am. Rev. Respir. Dis.*, **123**, 200.

Sacks, T., Moldow, C. W., Craddock, P. R., Bowers, T. K., and Jacobs, H. S. (1978). Oxygen radicals mediate endothelial cell damage by complement-stimulated granulocytes: An *in vitro* model of immune vascular damage. *J. Clin. Invest.*, **61**, 1161.

Sahebjami, H., Gawd, G., and Massaro, D. (1974). Influence of corticosteroids on recovery from oxygen toxicity. *Am. Int. Med.*, **110**, 577.

Saldeen, T. (1976). Trends in microvascular research. The microembolism syndrome. *Microvasc. Res.*, **11**, 227.

Schmidt, G. B., O'Neill, W. W., Koth, K., Hwang, K. K., Bennett, E. J., and Bombeck, C. T. (1978). Continuous positive airway pressure on the prophylaxis of the adult respiratory distress syndrome. *Surg. Gynecol. Obstet.*, **143**, 613.

Schneeberger-Keeley, E. E., and Karnovsky, M. J. (1968). The ultrastructural basis of alveolar-capillary membrane permeability to peroxidase used as a tracer. *J. Cell Biol.*, **37**, 781.

Schneider, R. C., Zapol, W. M., and Carvalho, A. (1980). Platelet consumption and sequestration in severe acute respiratory failure. *Am. Rev. Respir. Dis.*, **122**, 445.

Senior, R. M., Griffen, G. L., and Mecham, R. P. (1980). Chemotactic activity of elastin-derived peptides. *J. Clin. Invest.*, **66**, 859.

Sharf, S. M., Caldini, P., and Ingram, R. H. (1977). Cardiovascular effects of increasing airway pressure in the dog. *Am. J. Physiol.*, **232**, H35.

Shumer, W. (1976). Steroids in the treatment of septic shock. *Ann. Surg.*, **184**, 333.

Sibbald, W. J., Anderson, R. R., Reid, B., Holliday, R. L., and Driedger, A. A. (1981). Alveolar capillary permeability in human septic ARDS. *Chest*, **79**, 133.

Simpson, D. L., Goodman, M., Spector, S. L., and Petty, T. L. (1978). Long-term follow-up and bronchial reactivity testing in survivors of the adult respiratory distress syndrome. *Am. Rev. Respir. Dis.*, **117**, 449.

Starling, E. H., (1896). On the absorption of fluids from the connective tissue spaces. *J. Physiol.* (*Lond.*), **19**, 312.

Staub, N. C. (1974). Pulmonary edema. *Physiol. Rev.*, **54**, 678.

—— (1980). The pathogenesis of pulmonary edema. *Progr. Cardiovasc. Dis.*, **23**, 53.

—— Nagano, H., and Pearce, M. L. (1967). Pulmonary edema in dogs, especially the sequence of fluid accumulation in lungs. *J. Appl. Physiol.*, **22**, 227.

Steir, M., Ching, N., Roberts, E. B., and Nealon, T. F. (1974). Pneumothorax complicating continuous ventilatory support. *J. Thorac. Cardiovasc. Surg.*, **67**, 17.

Stothert, J. C. jr, and Carrico, C. J. (1981). Fluid therapy in adult respiratory distress syndrome: A pathophysiologic approach. *Sem. Resp. Med.*, **2**, 123.

Sugarman, H. J., Rogers, R. M., and Miller, L. D. (1972). Positive end-expiratory pressure (PEEP): Indications and physiologic considerations. *Chest*, **62**, (Suppl. 2), 86S.

Suter, P. M., Fairley, H. B., and Isenberg, M. D. (1975). Optimum end-expiratory airway pressure in patients with acute pulmonary failure. *N. Engl. J. Med.*, **292**, 284.

Swan, H. J. C., Ganz, W., Forrester, J., Marcus, H., Diamond, G., and Chonette, D. (1970). Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. *N. Engl. J. Med.*, **283**, 447.

Sykes, M. K., Young, W. E., and Robinson, B. E. (1965). Oxygenation during anaesthesia with controlled ventilation. *Br. J. Anaesth.*, **37**, 314.

Visick, W. D., Fairley, H. B., and Hickey, R. F. (1973). The effects of tidal volume and end-expiratory pressure on pulmonary gas exchange during anesthesia. *Anesthesiology*, **39**, 285.

Vreim, C. E., and Staub, N. C. (1976). Protein composition of lung fields in acute alloxan edema in dogs. *Am. J. Physiol.*, **230**, 376.

Weigelt, J. A., Mitchell, R. A., and Snyder, W. H. III (1979). Early positive end-expiratory pressure in the adult respiratory distress syndrome. *Arch. Surg.*, **114**, 497.

Weissmann, G., Smolen, J. E., and Korchak, H. M. (1980). Release of inflammatory mediators from stimulated neutrophils. *N. Engl. J. Med.*, **303**, 27.

Wilson, J. W. (1972). Treatment or prevention of pulmonary cellular damage with pharmacologic doses of corticosteroid. *Surg. Gynecol. Obstet.*, **134**, 675.

Yahav, J., Lieberman, P., and Molho, M. (1978). Pulmonary function following the adult respiratory distress syndrome. *Chest*, **74**, 247.

Yernault, J. C., Englert, M., and Sergysels, R. (1977). Follow-up of pulmonary function after "shock lung". *Bull. Eur. Physiopathol. Resp.*, **13**, 241.

Zapol, W. M., and Snider, M. T. (1980). Membrane lungs for acute respiratory failure: Current states. *Am. Rev. Respir. Dis.*, **121**, 907.

—— —— Hill, J. D., Fallat, R. J., Bardslett, R. H., Edmunds, L. H., Morris, A. H., Pierce, E. C., Thomas, A. N., Proctor, H. J., Drinker, P. A., Pratt, P. C., Bagniewski, A., and Miller, R. G. (1979). Extracorporeal membrane oxygenation in severe acute respiratory failure: A randomized prospective study. *J.A.M.A.*, **242**, 2193.

*Br. J. Anaesth.* (1982), **54**, 737

# OXYGEN TOXICITY OF THE LUNG: AN UPDATE

S. M. Deneke and B. L. Fanburg

The uses of high concentrations of therapeutic oxygen have expanded in recent decades. This situation came about both from the introduction of ventilation by intubation in the Intensive Care setting and with the use of hyperbaric oxygen for the treatment of anaerobic infections. Furthermore, high concentrations of oxygen have been used in deep sea diving and in aviation and space exploration. With potential side-effects of exposure to high concentrations of oxygen it has become increasingly important to understand better the parameters of exposure that produce toxicity, the mechanisms by which it occurs and the potential protective devices against its tissue-damaging effects. It is the purpose of this review to address these considerations. The reader is also referred to other reviews (Clark and Lambertsen, 1971; Mustafa and Tierney, 1978; Deneke and Fanburg, 1980a; Fisher, 1980; Frank and Massaro, 1980) where certain aspects of the subject may be covered in more detail.

Damage to tissues by oxygen seems to be related more to the partial pressure of oxygen than to its percent concentration. Hence, a high concentration of oxygen may be less damaging at high altitude where the atmospheric pressure is reduced than it is for the same concentration at normobaric pressure. The primary target of injury for normobaric hyperoxia is the lung, probably at least in part because lung cells are exposed to higher partial pressures of oxygen than are other cells of the body. With hyperbaric hyperoxia, the rapid onset of convulsions indicates that the central nervous system shows the earliest signs of toxicity. Hence, with higher partial pressures of oxygen than can be achieved under normobaric conditions, tissues of the central nervous system seem to be "more sensitive" than do cells of the lung. It is likely that certain cells of the body, even within the same organ, are more sensitive than others to hyperoxia.

Concentrations (or partial pressures) of oxygen that cause toxicity to living tissues are variable. Plants, at least at stages of mature growth, seem to be more resistant than animals to hyperoxia (Matkovics, 1977). Similarly, aerobic bacteria are more resistant to hyperoxia than are anaerobic ones (McCord, Keele and Fridovich, 1971). In the animal kingdom there is a wide variety of susceptibility to hyperoxia. For example, amphibians may survive indefinitely when exposed to 100% oxygen at atmospheric pressures, while the rat or mouse succumbs within 3–4 days after exposure to the same concentration of oxygen (Clark and Lambertsen, 1971).

The precise concentration of oxygen that is toxic to man has, for obvious reasons, been difficult to establish and probably varies according to age, nutritional status, endocrinological status and the history of previous exposures to oxidants or other substances that may alter mechanisms protective against oxygen toxicity. Some data bearing on physiological and pathological alterations in man exposed to hyperoxia are noted in table I. Needless to say, these data are not precise and provide only guidelines for predicting oxygen toxicity in man exposed to hyperoxia. Although Van De Water and his associates (1970) were unable to find physiological, radiological, or symptomatic alterations in normal subjects exposed to 100% oxygen for 6–12 h, Sackner and associates (1975) have reported the occurrence of tracheitis and decreased velocity of tracheal clearance of mucus in normal men exposed to 90–95% oxygen for 6 h. Comroe and others (1945) reported a decreased vital capacity for persons exposed to 100% oxygen for 25 h at sea level. Several physiological alterations, including increased wasted ventilation, increased arteriovenous shunting, decreased static and dynamic compliance and decreased diffusing capacity, have been reported to occur in man exposed to hyperoxia for 24–48 h.

It seems reasonable to conclude from these studies that individuals exposed to 100% oxygen at

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TABLE I. *Normobaric oxygen toxicity in man*

| Duration of exposure to 100% $O_2$ (h) | Changes | Reference |
|---|---|---|
| 6–12 | No changes in $(P_{AO_2} - P_{aO_2})$, PA pressure, pulmonary resistance, cardiac output or pulmonary extravascular water | Van De Water and others (1970) |
| 21–44 | No detectable physiological alterations | Singer and others (1970) |
| 40 | ↑ Wasted ventilation and A–V shunting | Barber, Lee and Hamilton (1970) |
| 25 | ↓ Vital capacity | Comroe and others (1945) |
| 30–48 | Small change in static and dynamic compliance and in diffusing capacity | Caldwell and others (1966) |

normobaric pressures are very likely to incur damage to the lung produced by hyperoxia. The damaging effect may be reversible if exposure to hyperoxia is discontinued after 24–48 h. With more prolonged exposure, more pronounced and possibly irreversible changes occur and the damaging effects may be lethal within a few days. Similar damaging effects of hyperoxia are likely to occur, albeit at a slower rate, for concentrations of oxygen less than 100%. The "safe" concentration of oxygen for humans has not been adequately established, but for practical purposes currently it might be considered that there is a high likelihood of some significant form of oxygen toxicity to the lung at concentrations of oxygen greater than 60–70% at atmospheric pressure.

Whether or not values of hyperoxia less than 60–70%, when given for sufficiently long periods of time, may cause some degree of tissue injury is not known. Data concerning damage by smaller concentrations of oxygen would, of course, be very useful since it is these concentrations of oxygen that are used more frequently in the Intensive Care setting. Although data relating to effects of these lower concentrations of oxygen have been obtained in animal studies (Frank, 1981c; Hayatdavoudi et al., 1981), their direct applicability to human subjects is uncertain. Furthermore, there may be sufficient variability according to factors such as age, nutrition, endocrine status and previous exposures to oxidants, to cause the whole question to be extremely complex when projections are made for an individual patient. Therefore, rather than try to establish precise concentrations of oxygen that produce toxicity, it may be more productive to optimize conditions that protect against oxygen toxicity and to use only a concentration of oxygen necessary to achieve an "adequate" arterial $P_{O_2}$ in the clinical setting.

## BIOCHEMICAL REACTIONS INVOLVED IN OXYGEN TOXICITY

According to the free radical theory of oxygen toxicity, the agent responsible for cellular damage is not the $O_2$ molecule, but rather any of a number of oxygen radicals or peroxides generated intracellularly by accelerated metabolic processes during exposure to hyperoxia (Deneke and Fanburg, 1980a; Frank and Massaro, 1980). Metabolic reduction of oxygen can produce these toxic agents (table II).

TABLE II. *Biological reductions of oxygen*

| Reaction | Major sources |
|---|---|
| $O_2 + e^- \rightarrow O_2^{\cdot -}$ (superoxide) | Phagocytic cells<br>Mono-oxygenases<br>Xanthine oxidase reaction |
| $O_2 + 2e^- + 2H^+ \rightarrow H_2O_2$ (hydrogen peroxide) | Xanthine oxidase reaction<br>$O_2^{\cdot -}$ dismutation |
| $O_2 + 3e^- + 3H^+ \rightarrow H_2O + OH^{\cdot}$ (hydroxyl radical) | Fenton reaction |
| $O_2 + 4e^- + 4H^+ \rightarrow 2H_2O$ (water) | Cytochrome oxidase reaction |

Superoxide radical ($O_2^{\cdot -}$) is generated as part of the bactericidal function of phagocytes (Babior, Kipnes and Curnutte, 1973; Hoffman and Autor, 1980), as a result of microsomal oxidation reactions (Aust, Roerig and Pederson, 1972; Hirata and Hayaishi, 1977) and in many autoxidations of biological materials (Misra and Fridovich, 1972; Misra, 1974; Sligar et al., 1974). Superoxide may participate in some cellular oxidations (Bors, Saran and Czapski, 1980; Fee, 1980). It may also contribute to the formation of at least two other toxic oxidant species (Fridovich, 1978; Halliwell et al., 1980). $O_2^{\cdot -}$ spontaneously dismutes to hydrogen peroxide ($H_2O_2$) in acid or neutral solution by the following reactions: $2O_2^{\cdot -} + 2H^+ \rightarrow H_2O_2 + O_2$ (Fee and Valentine, 1977). Also, in the presence of iron, $O_2^{\cdot -}$ and $H_2O_2$ can produce the hydroxyl radical ($OH^{\cdot}$) as follows:

$$H^+ + O_2^{\cdot -} \xrightarrow{Fe} OH^{\cdot} + H_2O + O_2$$

(Halliwell, 1978; McCord and Day, 1978). Both $H_2O_2$ and $OH^{\cdot}$ have demonstrated biological activity (McCord and Fridovich, 1978). $OH^{\cdot}$ is very reactive and would not be able to diffuse far from the site of generation without reacting with some biological molecule. $H_2O_2$, which is less reactive, could diffuse through solutions or membranes to cause damage at small distances from its origin. The question of which oxygen radical species is responsible for a given type of oxygen damage is complicated by the fact that many of the primary reactions of $H_2O_2$ or $OH^{\cdot}$ result in the formation of cellular peroxides or free radical species. Peroxides also decompose to form other radicals *in vivo*. The net result is a cascade chain reaction which generally results in a complex mixture of oxidized products, making the analysis of initial events complex.

The types of damage caused by oxygen radicals include lipid peroxidation, oxidation of protein sulphhydryls and oxidation of nucleic acids (Borg et al., 1978; Fridovich, 1978). Thus, oxygen radicals can cause membrane damage, enzymic inactivation and genetic damage, and cell death may result from a wide variety of cellular injuries.

Natural defence mechanisms are designed to cope (presumably adequately) with radicals produced by normal oxygen tensions, although it has been speculated that various manifestations of ageing are results of chronic exposure to oxygen at normal tensions. At increased oxygen concentrations natural defences are overwhelmed, resulting in excess radical-related cell damage. When the rate of this damage exceeds the rate of repair, cell and organism death results.

Various compounds that act as free radical quenchers or antioxidants and several enzyme systems have been identified as protective against oxygen radicals and their resulting damage. Of primary importance is reduced glutathione (GSH), which is a preferential substrate for many oxidizing agents, thus sparing protein SH groups from oxidation (Kosower, 1976). GSH is also a substrate for glutathione peroxidase which converts $H_2O_2$ or lipid peroxides to water or non-toxic lipid hydroxides (Flohé, Günzler and Ladenstein, 1976). The oxidized glutathione (GSSG) is reduced by glutathione reductase. The source of reducing activity is NADPH generated by the oxidation of glucose-6-phosphate in the hexose monophosphate shunt metabolic pathway. These reactions are shown in figure 1.

Other cellular enzymes protective against free radicals produced by hyperoxia include superoxide dismutase (SOD) and catalase (Fridovich, 1978; McCord and Fridovich, 1978). Various types of SOD are found in nature. These differ both in structure and in the metal ligand in the active site. Bacterial SOD are iron or manganese enzymes. The mitochrondria of eucaryotic cells have a manganese SOD similar to that of bacteria. Cytoplasmic SOD is a copper–zinc enzyme. Until recently it was presumed that all organisms that reduced oxygen contained SOD, but various species of mycoplasma

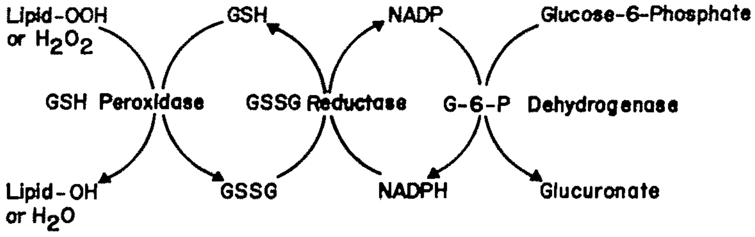

FIG. 1. Cellular enzyme systems protective against oxygen radicals.

have now been shown to carry out aerobic metabolism without protection from endogenous SOD (Lynch and Cole, 1980). Nevertheless, SOD undisputably has a major role in oxygen defences (Fridovich, 1978). SOD catalyses the reaction $2O_2^{-} + 2H^{+} \rightarrow H_2O_2 + O_2$. Catalase catalyses the reaction $2H_2O_2 \rightarrow 2H_2O + O_2$. Other cellular compounds identified as antioxidants and radical quenchers include ascorbic acid (vitamin C), cysteine and α-tocopherol (vitamin E). Biochemical studies of oxygen toxicity have tended to focus on changes in the various compounds and enzymes noted above to identify reasons for increased or decreased susceptibility to oxygen.

Lungs contain copper–zinc and manganese SOD, catalase, glutathione peroxidase, glutathione reductase, and glucose-6-phosphate dehydrogenase (Crapo and Tierney, 1974; Kimball et al., 1976). The amounts of these enzymes vary widely with species and age (Yam, Frank and Roberts, 1978). There is no apparent correlation between the absolute amounts of these enzymes and oxygen resistance among the various groups of animals studied. However, changes in concentrations of these enzymes within an animal are related to the development of tolerance to hyperoxia. This will be discussed further below.

## LUNG PATHOLOGY RESULTING FROM EXPOSURE TO HYPEROXIA

There seems to be a variability in the sensitivity of various cell types of the lung to toxic treatments such as hyperoxia. The particular cell type injured early in the process of toxicity may determine the chain of pathological events and the accompanying physiological alterations that follow exposure to hyperoxia. Attempts have been made to unravel the pathogenesis of cellular injury occurring as a result of exposure to hyperoxia. Although there is some evidence that airway mucosal cells may be injured by hyperoxia (Obara, Sekimoto and Iwai, 1979; Sackner et al., 1976), it appears that the primary pathological event is injury to the alveolar–capillary unit (Bowden and Adamson, 1974; Weibel, 1971). With careful longitudinal studies in animals, it appears that the endothelial cell and the Type I alveolar cell are the earliest sites of injury (Crapo et al., 1978, 1980) and injury to these cells may lead to sequential lung damage as a result of loss of integrity of the barrier between the alveolus and the capillary. At concentrations of 95–100% oxygen this damage is severe, resulting in a major loss of endothelium with accompanying oedema and subsequent death (Crapo et al., 1980). After prolonged exposure of animals to sublethal hyperoxia (60–85% oxygen), there are numerous non-specific pathological findings including the presence of atelectasis, oedema, alveolar haemorrhage, inflammation, fibrin deposition and thickening and hyalinization of alveolar membranes (Crapo et al., 1980; Chvapil and Peng, 1975).

The role of secondary cellular infiltration, such as that of leucocytes, in the pathogenesis of oxygen toxicity is uncertain. It has been postulated that leucocytes may be important in formation of free oxygen radicals that cause injury to the lung. Although it is well known from isolated cell studies that oxygen is quite toxic to lung cells in the absence of leucocytes, the leucocyte contribution may be important in producing the acute stages of oedema leading to death (Fox, Shasby et al., 1981).

With discontinuation of exposure to hyperoxia, at least two events may potentially develop as a result of the exposure. The first of these is the proliferation of the Type II alveolar cell that appears to constitute a restructuring of the alveoli of the lung (Crapo et al., 1978) and the second is a fibroblastic proliferation that may lead to interstitial fibrosis (Chvapil and Peng, 1975). The first event seems to be reparative in nature and may have the potential to produce a functional alveolar unit. Of course, capillary regeneration would also be required and little is known about this process. The production of fibrosis does not seem to have any utility in recovery and may be simply a manifestation of the aberrant proliferation of a cell type (the fibroblast) that is relatively insensitive to hyperoxia. Histological evidence of the tissue changes of injury and recovery may overlap one another.

Proliferation of the endothelium occurs in rats exposed to sublethal concentrations of oxygen (Crapo et al., 1978, 1980). Whether or not structural alterations such as this play a significant role in subsequent protection against hyperoxia is not known.

### In vitro *model systems*

Work done over the past several years using lung cells in culture has confirmed that individual cells exposed to hyperoxia can be killed without interactions with other cells. This has been most extensively demonstrated for endothelial cells and alveolar macrophages. Both macrophage phagocytic function and chemotaxis are damaged by values of hyperoxia as small as 40–60% (Simon, Axline and Robin, 1978; Raffin et al., 1980; Wolff et al., 1978;

Bowles, Dauber and Daniele, 1979). Endothelial cells derived from aorta or calf pulmonary arteries show evidence of impaired uptake of serotonin or α-aminoisobutyric acid by 24–72 h of exposure to 80–95% oxygen (Block and Stalcup, 1981; S. L. Lee and colleagues, unpublished data). Endothelial cells have also been shown to be damaged by morphological criteria within 24 h after exposure to 80% oxygen (Lee at al., 1982).

In addition to cell cultures, organ cultures and lung explants have been used to model the effects of oxygen on the lung. Cessation of ciliary activity has been shown in organ cultures of tracheal epithelium after 2–6 days of exposure to 60–80% oxygen (Boat, 1979).

Damage by hyperoxia has recently been reported in explants of parenchymal tissues from rat and rabbit lung (Boat, 1979; Martin et al., 1981). Release of a chromium-51 indicator from labelled lung tissue in culture showed that significant cell damage occurred within 18 h of exposure to 95% oxygen. The effects were prevented by SOD, catalase, ascorbate and α-tocopherol for the rat tissue and by catalase and α-tocopherol for the rabbit tissue.

A third *in vitro* model, the perfused lung, has proved to be a sensitive model to detect early functional damage to the pulmonary endothelium. Hyperoxia has been shown to impair the ability of the perfused lung to remove various compounds, including 5-hydroxytryptamine and prostaglandins, from the pulmonary circulation (Block and Fisher, 1977; Klein et al., 1978).

These *in vitro* systems have demonstrated that hyperoxia causes damage to individual lung cell types and to isolated lung tissues that is independent of any influx of cells from the circulation. However, oxygen radical production by activated PMN recruited to the lung during exposure to oxygen may be a significant factor in the resulting lung damage and death. Superoxide and hydrogen peroxide generated by PMN have been shown to cause damage to isolated endothelial cells *in vitro* (Sacks et al., 1978; Weiss et al., 1981). More recently, Repine and co-workers (Fox, Hoidal et al., 1981; Shasby et al., 1981; Harada et al., 1982) have reported: (a) correlations between PMN recruitment and lung damage in both rats and rabbits, (b) protection against hyperoxia death in rabbits by nitrogen mustard-induced neutropenia, and (c) the production of PMN chemotactic factors by oxygen-exposed rabbit macrophages which may be responsible for the influx of PMN into the lung. These data support a role for leucocyte $O_2^{-}$ in hyperoxic lung damage.

It has also been reported that SOD administered by constant infusion provides partial protection against oxygen damage in the lung (McLennan and Autor, 1978). This SOD would be expected to be most effective against extracellular superoxide sources such as that generated by activated leucocytes.

*Involvement of oxygen radicals*

A central question in confirming the oxygen radical mechanism proposed for oxygen toxicity is whether hyperoxia does indeed increase intracellular oxygen radical production. Freeman and coworkers have reported increases in $O_2^{-}$ production with increased exposure to oxygen in mitochondrial and microsomal fractions of rat lungs (Freeman and Crapo, 1981; Brown, Freeman and Crapo, 1981). Although increases in $O_2^{-}$ and other oxygen radicals have resisted measurement in intact cells and tissues, much indirect evidence exists that these radicals are indeed responsible for hyperoxic damage to cells. Enzymically-generated oxygen radicals have been shown to mimic hyperoxic damage to isolated cells as well as to perfused lung (Fox and Autor, 1978; Steinberg et al., 1979; Johnson et al., 1981; Tate et al., 1981). Also, inhibitors of oxygen radicals such as superoxide dismutase or thiourea and dimethylthiourea ($OH^{\cdot}$ quencher) have been shown to protect isolated cells, organ cultures and perfused lungs from oxygen damage (Block and Fisher, 1977; McLennan and Autor, 1978; Tate et al., 1981).

*Summary of events leading to hyperoxic death*

At the current time the chain of events leading to hyperoxia-induced death can be best summarized as shown in figure 2.

The relative importance of pathways a and b in figure 2 may depend on oxygen concentration, species or age, but it is likely that both internal and PMN-generated oxygen radicals contribute to the ultimate death of the animals.

## MECHANISMS OF DEVELOPMENT OF TOLERANCE TO HYPEROXIA

*General*

The ability to develop tolerance to oxygen exposures varies widely among animals (Clark and Lambertsen, 1971). Age and species affect both initial resistance to hyperoxia and the ability to increase resistance after various stimuli. Reasons for the

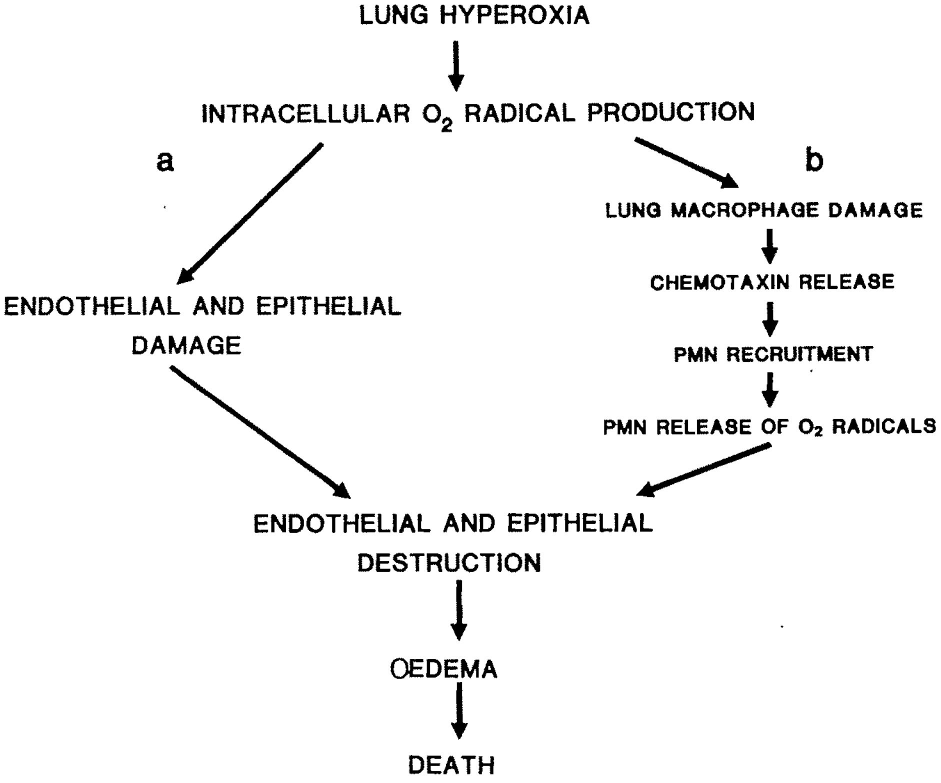
LUNG HYPEROXIA
INTRACELLULAR $O_2$ RADICAL PRODUCTION
a
b
LUNG MACROPHAGE DAMAGE
CHEMOTAXIN RELEASE
PMN RECRUITMENT
PMN RELEASE OF $O_2$ RADICALS
ENDOTHELIAL AND EPITHELIAL DAMAGE
ENDOTHELIAL AND EPITHELIAL DESTRUCTION
OEDEMA
DEATH

FIG. 2. Chain of events currently believed to lead to hyperoxia-induced death.

innate tolerance to oxygen of such animals as turtles, frogs and chickens are unknown but may be correlated with metabolic rate (Barthelemy, Belaud and Chastel, 1981). However, some mechanisms for variation in oxygen resistance in animals of different ages and for the differences in ability to develop tolerance have been at least partially explained.

*Age*

The young of many species are able to become tolerant to 100% oxygen rapidily enough to prevent death, even if the adult animals are killed by oxygen (Frank, Bucher and Roberts, 1978). The ability of these young animals to resist oxygen toxicity appears to be correlated with their ability to increase concentrations of protective enzymes in response to exposure to oxygen rapidly enough to prevent death (Frank, Bucher and Roberts, 1978; Bucher and Roberts, 1981). Various investigators have reported that significant increases, within 24–48 h, in concentrations of SOD, glucose-6-phosphate dehydrogenase, glutathione peroxidase and reductase, and in some cases of catalase, enable these animals to resist 100% oxygen. The observation appears to be species-specific since young rabbits, mice and rats show this response, while guineapigs and hamsters do not. Young guineapigs and hamsters, which are killed by 100% oxygen, cannot increase these enzymes soon enough to provide protection.

*Pre-treatment*

Adult small animals cannot react to 100% oxygen exposure rapidly enough to survive. However, the rat is capable of responding to 80–85% oxygen by increasing concentrations of SOD and the glutathione-related protective enzymes within 3–5 days of exposure (Crapo and Tierney, 1974; Kimball et al., 1976; Tierney, Yang and Ayers, 1975). The animals pre-exposed to a sublethal concentration of oxygen are able to tolerate prolonged exposures to 100% oxygen. Lung damage does occur, but the effects are not lethal in most cases. Unfortunately, toxic concentrations of oxygen are required for both increases in protective enzymes and the development of tolerance. Frank (1981c) has reported that pre-exposure of rats to 40–60% oxygen does not increase either protective enzyme concentrations or tolerance to subsequent exposure to 100% oxygen. In fact, these pre-exposures appear to increase the rate of damage caused by 100% oxygen, indicating that the lungs were already partially damaged by the exposure to lower concentrations of oxygen.

Other treatments that increase concentrations of protective enzymes in rats have also been found to increase tolerance to hyperoxia. These treatments will be discussed in detail in the next section. Thus, the common mechanism for development of tolerance to hyperoxia in adult rats, as well as in various neonatal animals, appears to be the stimulation of the production of the protective enzymes.

### *Cellular adaptation*

Attempts have been made to determine which lung cell types are responsible for the induction of enzymes and the development of tolerance to hyperoxia. The most definitive studies have been on the lung macrophage. Various investigators have shown that adult rat lung macrophages exposed to oxygen in tissue culture or *in vivo* do not increase concentrations of SOD (Stevens and Autor, 1977; Deneke, Bernstein and Fanburg, 1978). Macrophages of infant rats, however, have been shown to increase mitochrondrial SOD in response to exposure to hyperoxia *in vivo* or *in vitro* (Stevens and Autor, 1977; Autor and Stevens, 1980). Induction of SOD in cultured lung macrophages of adult mice has been reported as well as in macrophages isolated from guineapigs exposed to oxygen *in vivo* (Simon et al., 1977; Rister and Baehner, 1976). Thus, although there are instances of induction of SOD in adult lung macrophages, the induction does not correlate well with either induction of total lung SOD or with survival in hyperoxia.

More recently, Forman and Fisher (1981) have reported increases in mitochrondial SOD in lung Type II pneumocytes from rats exposed to oxygen *in vivo*, but not in cells exposed to hyperoxia *in vitro.* No changes were observed in other protective enzymes of these cells. Freeman, Mason and Crapo (1981), however, reported increases in several antioxidant enzyme concentrations in Type II cells isolated from lungs of rats exposed to oxygen. Confluent endothelial cells from pig pulmonary artery and aorta increase concentrations of SOD in response to hyperoxia (Ody et al., 1980). Many of the results obtained with cells in culture appear to be related to the source of the cells and to culture conditions, making it difficult at present clearly to relate these observed changes to mechanisms of adaptation of the lung to hyperoxia (Housset and Junod, 1981).

## FACTORS INFLUENCING TOLERANCE TO HYPEROXIA

### *General*

Several constitutional and environmental factors may influence tolerance to hyperoxia. Some factors which increase or decrease tolerance have rationales for their effects related to the biochemical mechanisms noted previously. Among factors best explored experimentally are metabolic alterations, diet, administered medications and chemicals and prior inhalation of oxygen itself. It is likely that the number of these factors will increase, but our current knowledge of them is discussed below.

### *Metabolic factors*

If the cause of hyperoxic damage is primarily oxygen radicals generated intracellularly by metabolic processes, factors that decrease metabolism, such as hypothyroid, hypothermic or hypopituitary states, might be expected to provide protection against hyperoxia.

Hypophysectomized rats have been reported to be more resistant to oxygen toxicity than normal controls (Bean and Smith, 1952). Hypothermia decreased retinal damage, but not lung damage, produced by hyperoxia in mice (Hellstrom and Nergardh, 1965). The rate of oxygen-induced rat lung damage has been reported to be a function of the temperature of the exposure chamber (McLennan and Autor, 1979). Hypothyroidism decreases oxygen utilization (Galton, 1978) and administration of thyroid hormone has been reported to increase oxygen toxicity in rats (Clark and Lambertsen, 1971).

### *Administered medications and chemicals*

Various drugs increase the rate of production of oxygen radicals (Hassan and Fridovich, 1979). Many of these drugs react by disrupting mitochondrial oxidative phosphorylation so as to result in increased production of $O_2^{\overline{\cdot}}$. Other drugs such as nitrofurantoin cause an increase in $O_2^{\overline{\cdot}}$ or $OH^{\cdot}$ production as part of their metabolism (Boyd et al., 1977). Some of these agents are indicated in table III. Many of these compounds have been found to increase the production of free radicals in mammalian cells *in vitro* or in bacteria, but only a few have been directly implicated in the increase in toxicity in animals or humans. Paraquat is the most widely investigated of these compounds (Fisher, Clements and Wright, 1973; Autor, 1974). There is some evidence that the lethal effect of Paraquat is not directly caused by free radical production, but rather by the resultant depletion of cellular NADPH (Forman, Nelson and Fisher, 1980).

Various drug treatments may also interfere with mechanisms protective against hyperoxia (Yam and Roberts, 1979). An often noted compound is diethyldithiocarbamate (DDC) that chelates copper and inhibits SOD (Frank, Wood and Roberts, 1978). Disulfiram (Antabuse) is metabolized to DDC. Disulfiram also reacts directly with protein sulphhydryls, therby inhibiting a wide variety of enzymes (Niems, Coffey and Hellerman, 1966). The exact mechanism by which disulfiram potentiates oxygen toxicity is unknown (Deneke, Bernstein and Fanburg, 1979; Forman, York and Fisher, 1980).

Other agents administered before or concomitant with oxygen exposure have been shown to produce tolerance to hyperoxia in rats. Prior injury with agents such as alphanapthylthiourea or oleic acid provides protection against hyperoxia (Tierney, Ayers and Kasuyama, 1977). Endotoxin administered concomitant with or slightly before exposure to hyperoxia also protects against toxicity by hyperoxia (Frank, Yam and Roberts, 1978: Frank, Summerville and Massaro, 1980). A near lethal dose of DDC given concomitantly with exposure to hyperoxia increases survival of rats and is accompanied by increases in glutathione-related enzymes, but not in SOD (Deneke and Fanburg, 1980, b).

The mechanism by which these treatments increase oxygen tolerance and tissue enzyme concentrations is not known, but may involve an early increase in cellular oxygen radical concentration or peroxidation which stimulates an increase in the enzymes rapidly enough to protect the lung. The induction of the protective enzymes by any of these agents has been shown only in adult rats. Adult mice, hamsters, rabbits or guineapigs apparently cannot increase protective enzyme concentrations in response to the agents (Frank, Bucher and Roberts, 1978; Lanir, Kerem and Gershon, 1981). Whether similar responses may occur in humans is not known.

TABLE III. *Potentiation of and protection against oxygen toxicity in the intensive care setting*

Potentiation
- (1) Hyperthyroidism
- (2) Hyperpyrexia
- (3) Dietary deficiency (protein, selenium, copper)
- (4) Drugs such as disulfiram (Antabuse), nitrofurantoin, ? chemotherapeutic agents
- (5) Exogenous agents such as Paraquat
- (6) Radiation

Protection
- (1) Avoidance of potentiators
- (2) Antioxidants such as ascorbate or α-tocopherol (in deficient patients)
- (3) ? superoxide dismutase
- (4) ? agent to stimulate protective enzymes such as endotoxin or diethyldithiocarbamate

### *Diet*

Deficiencies of several nutrients may decrease tolerance to exposure to hyperoxia. Administration of a diet deficient in protein to rats for 6 days produced an increased susceptibility to hyperoxia (Deneke, Gershoff and Fanburg, 1981a, b). The increased toxicity was reversed by the addition of cysteine, cystine or methionine to the diet. Rats on unsupplemented low protein diets could not increase concentrations of lung glutathione normally in response to oxygen exposure. It was concluded that the increased toxicity to hyperoxia in the protein-deficient animals was probably a result of the lack of a cysteine precursor necessary for the synthesis of the glutathione tripeptide. Addition of the supplementary amino acid to a normal protein diet did not confer added protection to these animals. Frank (1981a) has also reported increased oxygen sensitivity in undernourished newborn rats.

Deficiencies of vitamins or trace metals in diets have also been found to produce increased susceptibility of the experimental animal to hyperoxia. A deficiency of α-tocopherol produces increased oxygen toxicity, probably as a result of the ability of α-tocopherol to quench free radicals (Tierney, Ayers and Kasuyama, 1977). Similarly, deficiencies of the trace metals, copper or selenium, in the diet produce increased susceptibility to hyperoxia (Cross et al., 1977; Jenkinson, Lawrence and Burke, 1980). Copper is a component of the active site of cytoplasmic SOD and selenium is necessary for the activity of glutathione peroxidase. A diet of saturated fatty acids also appears to increase oxygen sensitivity in rats (Kehrer and Autor, 1978). Unfortunately, dietary supplementation with antioxidants or radical quenchers has not been found to increase survival in non-deficient animals exposed to hyperoxia.

### *Changes in oxygen concentrations*

Hypoxia, altitude acclimatization, sublethal hyperoxia and intermittent lethal hyperoxia have all been shown to stimulate the development of tolerance to hyperoxia in rats. The mechanism in each case seems to be similar. Hypoxia has been shown to increase concentrations of SOD and other protective enzymes (Frank, 1981b). Altitude acclimatization is essentially long-term exposure to hypoxia (Brauer et al., 1970). Sublethal hyperoxia, as stated earlier, stimulates protective enzymes, probably as a result of a response to increased tissue oxygen radicals. Intermittent exposure to 100% oxygen allows time for protective enzyme concentrations to increase before severe toxic effects occur (Hendricks et al., 1977; Paegle, Bernhard and Turndorf, 1977; Frank, 1981c).

## CONCLUSIONS

There is little likelihood of the immediate development of a substitute gas for oxygen or improved methods for delivery of oxygen to tissues at lower partial pressures. Therefore, the best current approaches to protection against oxygen toxicity are avoidance of potentiating substances or conditions and the development of protective compounds that are in themselves non-toxic. Although these approaches may be counterproductive in situations such as treatment of anaerobic infections, where the damaging effect of oxygen is needed for therapy, they are very appropriate in the Intensive Care setting where oxygen toxicity is only a byproduct of the treatment.

Methods to prevent potentiation of oxygen toxicity that have some established scientific validity and potential utility are noted in table III. These methods are directed toward the avoidance of circumstances, conditions or accompanying medications that may potentiate oxygen toxicity. It has been established in experimental animal models that factors that increase tissue metabolism, such as hyperpyrexia or hyperthyroidism potentiate oxygen toxicity (Clark and Lambertsen, 1971). Hence, it would seem reasonable to avoid increased body temperatures and to treat hyperthyroidism vigorously in patients who are being subjected to hyperoxia. Similarly, as also indicated previously in this review, certain nutritional alterations may potentiate toxicity resulting from hyperoxia. Despite adequate caloric replacements with carbohydrates, the administration of proteins is frequently reduced in patients in the Intensive Care setting. If animal experimental data can be applied to humans, it would seem appropriate to be certain that patients are receiving adequate intakes of sulphur-containing amino acids (Deneke, Gershoff and Fanburg, 1981a, b).

Avoidance of any substances or therapies that may potentiate oxygen toxicity are similarly important. In this context, it has been demonstrated in animals that disulfiram, a drug used for aversion therapy of alcoholism, potentiates oxygen toxicity. Although it is unlikely that this drug will be used with any regularity in an Intensive Care setting, the observation that it potentiates oxygen toxicity should be a warning that other drugs may produce a similar effect. A more likely drug to be used in the Intensive Care setting is the antibiotic nitrofurantoin. It is now recognized that this drug may produce lung toxicity by increasing oxygen free radical formation (Boyd et al., 1977). Whether or not concentrations of nitrofurantoin or similar drugs that may potentiate oxygen toxicity are ever achieved in humans is unknown, but it is theoretically possible. Chemotherapeutic agents and radiation therapy may have synergistic effects with those produced by hyperoxia, and these possibilities must be kept in mind when planning therapy for a patient in an Intensive Care setting.

It is known that the herbicide, Paraquat, increases superoxide radical production by the respiratory chain and is more toxic in hypoxia than normobaric environments (Fisher, Clements and Wright, 1973). Hence, administration of increased oxygen concentrations to a patient who has arrived in the Intensive Care setting as a result of ingestion of Paraquat may by counterproductive.

It has clearly been shown that the administration of non-lethal hyperoxia to experimental rats results in increased resistance to 100% oxygen by these animals. As noted earlier in this review, this is related to stimulation of enzymes protective against hyperoxia. It has also been shown that this effect is species-specific for the rat, at least in the experimental animal. If the strategy can be applied to the human, it would require graded administration of oxygen to patients. In a practical sense, this probably occurs in the Intensive Care Unit anyway since increase in concentrations of oxygen usually used in therapy are given incrementally because of the usual gradual deterioration of patients. Hence, it is unlikely that any further benefit will be achieved from use of a strategy that utilizes pre-exposure to nonlethal values of hyperoxia in the Intensive Care setting.

More promising may be the use of other substances that stimulate the formation of enzymes protective against formation of free oxygen radicals. Endotoxin (Frank, Summerville and Massaro, 1980) and diethyldithiocarbamate (Deneke and Fanburg, 1980b) are two such compounds that in combination with oxygen may stimulate enzymes protective against oxygen radicals and thereby induce resistance to tissue damage from these radicals. The use of diethyldithiocarbamate in experimental animals seems to require a dosage that is close to a toxicity value and therefore may not be practical in the Intensive Care setting. Whether or not endotoxin will have applicability to human subjects is not known. Since this compound is known also to produce toxic effects, modifications of it may be required before any testing in human subjects.

Although antioxidants such as ascorbate and α-tocopherol are clearly protective against hyperoxia in the vitamin-deficient animal, there has not yet been any evidence that supplementary doses of these antioxidants would be useful as a protective agent against hyperoxia in an individual who is not vitamin deficient.

The administration of superoxide dismutase would be an obvious protective mechanism against hyperoxic damage. McLennan and Autor (1978) have demonstrated that continuous intra-peritoneal infusion of superoxide dismutase confers some protection against pulmonary oxygen toxicity in the rat. There has been at least one report on the administration of this enzyme in the neonate (Rosenfeld et al., 1980).

## REFERENCES

Aust, S. D., Roerig, C. L., and Pederson, T. C. (1972). Evidence for superoxide generation by NADPH-cytochrome-c reductase of rat liver microsomes. *Biochem. Biophys. Res. Commun.*, 47, 1133.

Autor, A. P. (1974). Reduction of Paraquat toxicity by superoxide dismutase. *Life Sci.*, 14, 1309.

—— Stevens, J. B. (1980). *Chemical and Biochemical Aspects of Superoxide and Superoxide Dismutase Developments in Biochemistry*, Volume 11A, p. 104. New York: Elsevier/North Holland.

Babior, B. M., Kipnes, R. S., and Curnutte, J. T. (1973). Biological defense mechanisms: The production by leukocytes of superoxide, a potential bactericidal agent. *J. Clin. Invest.*, 52, 741.

Barber, R. E., Lee, J., and Hamilton, W. K. (1970). Oxygen toxicity in man. A prospective study in patients with irreversible brain damage. *N. Eng. J. Med.*, 283, 1478.

Barthelemy, L., Belaud, A., and Chastel, C. (1981). A comparative study of oxygen toxicity in vertebrates. *Respir. Physiol.*, 44, 261.

Bean, J. W., and Smith, C. W. (1952). Hypophyseal and adrenocortical factors in pulmonary damage induced by oxygen at atmospheric pressure. *Am. J. Physiol.*, 172, 169.

Block, E. R., and Fisher, A. B. (1977). Prevention of hyperoxic-induced depression of pulmonary serotonin clearance by pretreatment with superoxide dismutase. *Am. Rev. Respir. Dis.*, 116, 441.

—— Stalcup, S. A. (1981). Depression of serotonin uptake by cultured endothelial cells exposed to high $O_2$ tension. *J. Appl. Physiol.*, 50, 1212.

Boat, T. F. (1979). Studies of oxygen toxicity in cultured human neonatal respiratory epithelium. *J. Pediatr.*, 95, 916.

Borg, D. C., Schaich, R. M., Elmore, J. J., and Bell, J. A. (1978). Cytotoxic reactions of free radical species of oxygen. *Photochem. Photobiol.*, 28, 803.

Bors, W., Saran, M., and Czapski, G. (1980). *Biological and Clinical Aspects of Superoxide and Superoxide Dismutase. Developments in Biochemistry*, Volume 11B, p. 1. New York: Elsevier/North Holland.

Bowden, D. H., and Adamson, I. Y. R. (1974). Endothelial regeneration as a marker of the differential vascular responses in oxygen-induced pulmonary edema. *Lab. Invest.*, 30, 350.

Bowles, K. L., Dauber, J. H., and Daniele, R. P. (1979). The effect of hyperoxia on migration of alveolar macrophages *in vitro*. *Am. Rev. Respir. Dis.*, 120, 541.

Boyd, M., Sasame, H., Mitchell, J., and Catignani, G. (1977). Dose-dependent toxicity by nitrofurantoin (NF) and modification by vitamin E, dietary fat and oxygen. *Fed. Proc.*, 36, 45.

Brauer, R. W., Parrish, E. E., Way, R. O., Pratt, P. C., and Pessotti, R. L. (1970). Protection by altitude acclimatization against lung damage from exposure to oxygen at 825 mm Hg. *J. Appl. Physiol.*, 28, 474.

Brown, P. C., Freeman, B. A., and Crapo, J. D. (1981). The effect of hyperoxia on oxygen consumption and free radical production in rat lung microsomes. *Fed. Proc.*, 40, 426.

Bucher, J. R., and Roberts, R. J. (1981). The development of newborn rat lung in hyperoxia: a dose-dependent study of lung growth, maturation and changes in antioxidant enzyme activities. *Pediatr. Res.*, 15, 999.

Caldwell, P. R. B., Lee, W. L., Schildkraut, H. S., and Archibald, E. R. (1966). Changes in lung volume, diffusing capacity and blood gases in man breathing oxygen. *J. Appl. Physiol.*, 21, 1477.

Chvapil, M., and Peng, Y. M. (1975). Oxygen and lung fibrosis. *Arch. Environ. Health*, 30, 528.

Clark, J. M., and Lambertsen, C. J. (1971). Pulmonary oxygen toxicity: A review. *Pharmacol. Rev.*, 23, 37.

Comroe, J. H. jr, Dripps, R. D., Dumke, P. R., and Deming, M. (1945). Oxygen toxicity: The effect of inhalation of high concentrations of oxygen for twenty-four hours on normal man at sea level and at a simulated altitude of 18 000 feet. *J.A.M.A.*, 128, 710.

Crapo, J. D., Barry, B. E., Foscue, H. A., and Shelburne, J. (1980). Structural and biochemical changes in rat lungs occurring during exposures to lethal and adaptive doses of oxygen. *Am. Rev. Respir. Dis.*, 122, 123.

—— Marsh-Salin, J., Ingram, P., and Pratt, P. C. (1978).

Tolerance and cross-tolerance using $NO_2$ and $O_2$. II pulmonary morphology and morphometry. *J. Appl. Physiol.*, **44**, 370.

—— Tierney, D. F. (1974). Superoxide dismutase and pulmonary oxygen toxicity. *Am. J. Physiol.*, **226**, 1401.

Cross, C. E., Hasagewa, G., Reddy, K. A., and Omaye, S. T. (1977). Enhanced lung toxicity of $O_2$ in selenium-deficient rats. *Res. Commun. Chem. Pathol. Pharmacol.*, **16**, 695.

Deneke, S. M., Bernstein, S., and Fanburg, B. L. (1978). Absence of inductive effects of hyperoxia on superoxide dismutase activity in alveolar macrophages. *Am. Rev. Respir. Dis.*, **118**, 105.

—— —— —— (1979). Enhancement by disulfiram (Antabuse) of toxic effects of 95 to 97% $O_2$ on the rat lung. *J. Pharmacol. Exp. Ther.*, **208**, 377.

—— Fanburg, B. L. (1980a). Normobaric oxygen toxicity of the lung. *N. Engl. J. Med.*, **303**, 76.

—— —— (1980b). Involvement of glutathione enzymes in $O_2$ tolerance development by diethyldithiocarbamate. *Biochem. Pharmacol.*, **71**, 1367.

—— Gershoff, S. N., and Fanburg, B. L. (1981a). Protein deficiency and increased oxygen toxicity in rats. *Fed. Proc.*, **40**, 427.

—— —— —— (1981b). Low protein diet enhancement of oxygen toxicity reversed by cystine, cysteine or methionine. *Clin. Res.*, **29**, 685.

Fee, J. A. (1980). *Biological and Clinical Aspects of Superoxide and Superoxide Dismutase. Developments in Biochemistry*, Volume 11B, p. 41. New York: Elsevier/North Holland.

—— Valentine, J. S. (1977). *Superoxide and Superoxide Dismutase* (eds A. M. Michelson, J. M. McCord and I. Fridovich), p. 19. New York: Academic Press.

Fisher, A. B. (1980). Oxygen therapy, side effects and toxicity. *Am. Rev. Respir. Dis.*, **122**, 61.

Fisher, H. K., Clements, J. A., and Wright, R. R. (1973). Enhancement of oxygen toxicity by the herbicide paraquat. *Am. Rev. Respir. Dis.*, **107**, 246.

Flohé, L., Günzler, W. A., and Ladenstein, R. (1976). *Gluthathione Metabolism and Function*, p. 115. New York: Raven Press.

Forman, H. J., and Fisher, A. B. (1981). Antioxidant enzymes of rat granular pneumocytes, constitutive levels and effect of hyperoxia. *Lab. Invest.*, **45**, 1.

—— Nelson, J., and Fisher, A. B. (1980). Rat alveolar macrophages require NADPH for superoxide production in the respiratory burst. Effect of NADPH depletion by paraquat. *J. Biol. Chem.*, **225**, 9879.

—— York, J. L., and Fisher, A. B. (1980). Mechanism for the potentiation of oxygen toxicity by disulfiram. *J. Pharmacol. Exp. Ther.*, **212**, 452.

Fox, A. W., and Autor, A. P. (1978). Superoxide anion mediated toxicity in isolated lung cell preparations. *Am. Rev. Respir. Dis.*, **117**, 337.

Fox, R. B., Hoidal, J. R., Brown, D. M., and Repine, J. E. (1981). Pulmonary inflammation due to oxygen toxicity: involvement of chemotactic factors and polymorphonuclear leukocytes. *Am. Rev. Respir. Dis.*, **123**, 521.

—— Shasby, D. M., Harada, R. N., and Repine, J. E. (1981). A novel mechanism for pulmonary oxygen toxicity: Phagocyte mediated lung injury. *Chest*, **80S**, 3S.

Frank, L. (1981a). Undernutrition in newborn rats compromises their tolerance to prolonged hyperoxia. *Am. Rev. Respir. Dis.*, **123**, (Suppl.), 156.

—— (1981b). Pre-exposure to hypoxia (10% oxygen) pulmonary toxicity, species differences and role of the lung antioxidant enzymes. *Clin. Res.*, **29**, 550A.

—— (1981c). Endotoxin reverses the decreased tolerance of rats to 95% $O_2$ after pre-exposure to lower $O_2$. *J. Appl. Physiol.*, **51**, 557.

—— Bucher, J. R., and Roberts, R. J. (1978). Oxygen toxicity in neonatal and adult animals of various species. *J. Appl. Physiol.*, **45**, 699.

—— Massaro, D. (1980). Oxygen toxicity. *Am. J. Med.*, **69**, 117.

—— Summerville, J., and Massaro, J. (1980). Protection from oxygen toxicity with endotoxin. Role of the endogenous antioxidant enzymes of the lung. *J. Clin. Invest.*, **65**, 104.

—— Wood, D. L., and Roberts, R. J. (1978). Effects of diethyldithiocarbamate on oxygen toxicity and lung enzyme activity in immature and adult rats. *Biochem. Pharmacol.*, **27**, 251.

—— Yam, J., and Roberts, R. J. (1978). The role of endotoxin in protection of adult rats from oxygen-induced lung toxicity. *J. Clin. Invest.*, **61**, 269.

Freeman, B. A., and Crapo, J. D. (1981). Hyperoxia increases oxygen radical production in rat lungs and lung mitochondria. *J. Biol. Chem.*, **256**, 10986.

—— Mason, R. J., and Crapo, J. D. (1981). Induction of antioxidant enzymes in alveolar type II cells following exposure of rats to hyperoxia. *Fed. Proc.*, **40**, 230.

Fridovich, I. (1978). The biology of oxygen radicals. *Science*, **201**, 875.

Galton, V. A. (1978). Role of thyroid gland in oxygen toxicity. *Am. J. Physiol.*, **235**, E628.

Halliwell, B. (1978). Superoxide-dependent formation of hydroxyl radicals in the presence of iron chelates. *FEBS Lett.*, **92**, 321.

—— Richmond, R., Wong, J. F., and Gutteridge, J. M. C. (1980). *Biological and Clinical Aspects of Superoxide and Superoxide Dismutase. Developments in Biochemistry.* Volume 11B, p. 32. New York: Elsevier/North Holland.

Harada, R. N., Bowman, C. M., Fox, R. B., and Repine, J. E. (1982). Alveolar macrophage secretions: initiators of inflammation in pulmonary oxygen toxicity. *Chest*, (in press).

Hassan, H. M., and Fridovich, I. (1979). Intracellular production of superoxide radical and of hydrogen peroxide by redox active compounds. *Arch. Biochem. Biophys.*, **196**, 385.

Hayatdavoudi, G., O'Neill, J. J., Barry, B. E., Freeman, B. A., Crapo, J. D. (1981). Pulmonary injury in rats following a continuous exposure to 60% $O_2$ for 7 days. *J. Appl. Physiol.*, **51**, 1220.

Hellström, B., and Nergardh, A., (1965). The effect of high oxygen concentrations and hypothermia on the lung of the newborn mouse. *Acta Paediatr. Scand.*, **54**, 457.

Hendricks, P. L., Hall, D. A., Hunter, W. L., and Haley, P. J. (1977). Extension of pulmonary $O_2$ tolerance in man at 2 ATA by intermittent $O_2$ exposure. *J. Appl. Physiol.*, **41**, 593.

Hirata, F., and Hayaishi, O. (1977). *Superoxide and Superoxide Dismutases* (eds A. M. Michelson, J. M. McCord and I. Fridovich), p. 395. New York: Academic Press.

Hoffman, M., and Autor, A. P. (1980). Production of superoxide anion by an NADPH-oxidase from rat pulmonary macrophages. *FEBS Lett.*, **121**, 352.

Housset, B., and Junod, A. F. (1981). Superoxide dismutase (SOD) catalase (CAT) and glutathione peroxidase (GP) in cultured pig aortic (AO) and pulmonary artery (PA) endothelial cells (EC). Effects of hyperoxia. *Am. Rev. Respir. Dis.*, **123**, 218.

Jenkinson, S. G., Lawrence, R. A., and Burke, R. F. (1980).

Enhanced lung toxicity of oxygen in copper deficient rats. *Am. Rev. Respir. Dis.*, **121**, 224.

Johnson, K. J., Fantone, J. C., Kaplan, J., and Ward, P. A. (1981). *In vivo* damage of rat lungs by oxygen metabolism. *J. Clin. Invest.*, **47**, 983.

Kehrer, J. P., and Autor, A. P. (1978). The effect of dietary fatty acids on the composition of adult rat lung lipids: relationship to oxygen toxicity. *Toxicol. Appl. Pharmacol.*, **44**, 423.

Kimball, R. E., Reddy, K., Peirce, T. H., Schwartz, L. W., Mustafa, M. D., and Cross, C. E. (1976). Oxygen toxicity: augmentation of antioxidant defense mechanisms in rat lung. *Am. J. Physiol.*, **230**, 1425.

Klein, L. S., Fisher, A. B., Soltoff, S., and Coburn, R. F. (1978). Effect of $O_2$ exposure on pulmonary metabolism of prostaglandin $E_2$. *Am. Rev. Respir. Dis.*, **118**, 622.

Kosower, E. M. (1976). *Glutathione: Metabolism and Function*, p. 1. New York: Raven Press.

Lanir, A., Kerem, D., and Gershon, D. (1981). Pulmonary oxygen toxicity: lack of tolerance of mice of various ages. *Biochem. Biophys. Res. Commun.*, **101**, 1193.

Lee, S. L., Douglas, W. J. H., Deneke, S. M., and Fanburg, B. L. (1982). Ultrastructural morphology of bovine artery endothelial cells exposed to hyperoxia *in vivo*. *Clin. Res.*, **30**, 434.

Lynch, R. E., and Cole, B. C. (1980). *Mycoplasma pneumoniae*: a prokaryote which consumes oxygen and generates superoxide but which lacks superoxide dismutase. *Biochem. Biophys. Res. Commun.*, **96**, 98.

McCord, J. M., and Day, E. D. (1978). Superoxide-dependent production of hydroxyl radical catalysed by iron-EDTA complex. *FEBS Lett.*, **86**, 139.

—— Fridovich, I. (1978). The biology and pathology of oxygen radicals. *Ann. Intern. Med.*, **89**, 122.

—— Keele, B. B. jr., and Fridovich, I. (1971). An enzyme-based theory of obligate anaerobiosis: the physiological function of superoxide dismutase. *Proc. Natl. Acad. Sci. U.S.A.*, **68**, 1024.

McLennan, G., and Autor, A. P. (1978). Effects of continuous intra-peritoneal infusion of superoxide dismutase on pulmonary oxygen toxicity in the rat. *Am. Rev. Respir. Dis.*, **117**, 371.

—— —— (1979). Effect of temperature on pulmonary oxygen toxicity. *Am. Rev. Respir. Dis.*, **119**, 150.

Martin, W. J., James, E. G., Hunninghake, G. W., and Crystal, R. G. (1981). Oxidant injury of lung parenchymal cells. *J. Clin. Invest.*, **68**, 1277.

Matkovics, B. (1977). *Superoxide and Superoxide Dismutases* (eds A. M. Michelson, J. M. McCord and I. Fridovich), p. 50. New York: Academic Press.

Misra, H. P. (1974). Generation of superoxide free radical during the autoxidation of thiols. *J. Biol. Chem.*, **249**, 2151.

—— Fridovich, I. (1972). The generation of superoxide radical during the autoxidation of hemoglobin. *J. Biol. Chem.*, **247**, 6968.

Mustafa, M. G., and Tierney, D. F. (1978). Biochemical and metabolic changes in the lung with oxygen, ozone and nitrogen dioxide toxicity. *Am. Rev. Respir. Dis.*, **118**, 1061.

Niems, A. H., Coffey, D. S., and Hellerman, L. (1966). A sensitive radioassay for sulfhydryl groups with tetraethylthiuram disulfide. *J. Biol. Chem.*, **241**, 3036.

Obara, H., Sekimoto, M., and Iwai, S. (1979). Alterations to the bronchial and bronchiolar surfaces of adult mice after exposure to high concentrations of oxygen. *Thorax*, **34**, 479.

Ody, C., Bach-Dieterle, Y., Wand, I., and Junod, A. F. (1980). Effect of hyperoxia on superoxide dismutase content of pig, pulmonary artery and aortic endothelial cells in culture. *Exp. Lung Res.*, **1**, 271.

Paegle, R. D., Bernhard, W. N., and Turndorf, H. (1977). Intermittent exposure to 40 percent oxygen prolongs rat survival in 100 percent oxygen. *Anesth. Analg.* (Cleve.), **56**, 851.

Raffin, T. A., Simon, L. M., Braun, D., Theodore, J., and Robin, E. D. (1980). Impairment of phagocytosis by moderate hyperoxia (40–60 percent oxygen) in lung macrophages. *Lab. Invest.*, **42**, 622.

Rister, M., and Baehner, R. L. (1976). The alteration of superoxide dismutase, catalase, glutathione peroxidase and NAD(P)H cytochrome-c reduction in guinea pigs polymorphonuclear leukocytes and alveolar macrophages during hyperoxia. *J. Clin. Invest.*, **58**, 1174.

Rosenfeld, W., Evans, H., Salazar, D., and Jhaveri, R. (1980). Use of superoxide dismutase in neonates with severe respiratory distress syndrome. *Clin. Res.*, **28**, 654A.

Sackner, M. A., Hirsch, J. H., Epstein, S., and Rywlin, A. M. (1976). Effect of oxygen in graded concentrations upon tracheal mucous velocity. *Chest*, **69**, 164.

—— Landa, J., Hirsch, J., and Zapata, A. (1975). Pulmonary effects of oxygen breathing; a 6-hour study in normal men. *Ann. Intern. Med.*, **82**, 40.

Sacks, T., Moldow, C. F., Craddock, P. P., Bowers, T. K., and Jacob, H. S. (1978). Oxygen radicals mediate endothelial cell damage by complement-stimulated granulocytes. *J. Clin. Invest.*, **61**, 1161.

Shasby, D. M., Shasby, S. S., Bowman, C. M., Fox, R. B., Harada, R. M., Tate, R. M., and Repine, J. E. (1981). Angiotensin converting enzyme concentrations in the lung lavage of normal rabbits, and rabbits treated with nitrogen mustard exposed to hyperoxia. *Am. Rev. Respir. Dis.*, **124**, 202.

Simon, L. M., Axline, S. G., and Robin, E. D. (1978). The effect of hyperoxia on phagocytosis and pinocytosis in isolated pulmonary macrophages. *Lab. Invest.*, **39**, 541.

—— Liu, J., Theodore, J., and Robin, E. D. (1977). Effect of hyperoxia on superoxide dismutase activity in rat alveolar macrophages. *Am. Rev. Respir. Dis.*, **115**, 279.

Singer, M. M., Wright, F., Stanley, L. K., Roc, B. B., and Hamilton, W. K. (1970). Oxygen toxicity in man. A prospective study in patients after open heart surgery. *N. Engl. J. Med.*, **283**, 1473.

Sligar, S. G., Lipscomb, J. D., Debrunner, P. G., and Gunsalus, I. C. (1974). Superoxide anion production by the autoxidation of cytochrome P-450. *Biochem. Biophys. Res. Commun.*, **61**, 290.

Steinberg, H., Das, D. K., Moy, W., Eglow, R., and Greenwald, R. (1979). Injury to pulmonary endothelium induced by superoxide radical. *Am. Rev. Respir. Dis.*, **119**, 364.

Stevens, J. B., and Autor, A. P. (1977). Oxygen-induced synthesis of superoxide dismutase and catalase in pulmonary macrophages of neonatal rats. *Lab. Invest.*, **37**, 470.

Tate, R. M., Van Benthuysen, K. M., Shasby, D. M., McMurtz, I. F., Bowman, C. M., Harada, R. N., Fox, R. B., and Repine, J. E. (1981). Dimethylthiourea, a hydroxyl radical scavenger, blocks oxygen radical-induced acute edematous lung injury in an isolated perfused lung. *Am. Rev. Respir. Dis.*, **123**, (Suppl.), 243.

Tierney, D. F., Ayers, L., and Kasuyama, R. S. (1977). Altered sensitivity to oxygen toxicity. *Am. Rev. Respir. Dis.*, **115**, 595.

—— Yang, J., and Ayers, L. (1975). Enzymatic activity in rat lungs. Some changes with exposure to 1 atm. oxygen. *Chest*, **67**, 40S.

Van De Water, J. N., Kagey, K. S., Miller, I. T., Parker, D. A., O'Connor, N. E., Sheh, J., MacArthur, J. D., Zollingor, R. M., and Moore, F. D. (1970). Response of the lung to six to 12 hours of 100 percent oxygen inhalation in normal man. *N. Engl. J. Med.*, **283**, 1473.

Weibel, E. R. (1971). Oxygen effect on lung cells. *Arch. Intern. Med.*, **128**, 54.

Weiss, S. J., Young, J., LoBuglio, A. F., Slovka, A., and Nimeh, N. F. (1981). Role of hydrogen peroxide in neutrophil mediated destruction of cultured endothelial cells. *J. Clin. Invest.*, **68**, 714.

Wolff, L. J., Boxer, L. A., Allen, J. M., and Baehner, R. L. (1978). The selective effect of hyperoxia on the guinea pig alveolar macrophage membrane. *J. Reticuloendothel. Soc.*, **24**, 377.

Yam, J., Frank, L., and Roberts, R. J. (1978). Oxygen toxicity: comparison of lung biochemical responses in neonatal and adult rats. *Pediatr. Res.*, **12**, 115.

—— Roberts, R. J. (1979). Pharmacological alteration of oxygen-induced lung toxicity. *Toxicol. Appl. Pharmacol.*, **47**, 367.

*Br. J. Anaesth.* (1982), **54**, 751

# ASSESSMENT OF PULMONARY AIRWAY CALIBRE

J. R. LEHANE

The assessment of airway calibre is of relevance to anaesthetic practice for the following reasons. Clinical management of patients before or after anaesthesia and during intensive respiratory care often requires information about the degree of patency of airways. Following induction of general anaesthesia there may be considerable difficulty in inflating the lungs and this may be interpreted either as an increase in airways resistance or as a decrease in compliance. Clinical criteria do not enable a distinction to be made between these two entities. When measurements of resistance are made during general anaesthesia we have shown (Lehane, Jordan and Jones, 1980) that large changes occur which are undetectable clinically. Many drugs used in anaesthetic practice may influence airway calibre and methods are required for evaluating these effects in both conscious and anaesthetized patients.

## PHYSIOLOGICAL BACKGROUND

In reviewing the methods available for the assessment of airway calibre it is first necessary to understand the mechanisms which determine static airway dimensions and the ways in which gas flow modifies them.

The static dimensions of the pulmonary airways, that is their dimensions when there is no gas flow, are determined by the interaction of the *elastic recoil* of the lungs and the *elastic properties* of the airways. When gas flows along the airways pressure gradients are introduced which tend to distend or compress the airways from their static dimensions.

### *Elastic recoil*

The elastic recoil of the lungs can be demonstrated by opening the pleural cavity and noting that the lung recoils away from the parietal pleura, expelling air through the trachea as it does so. This recoil is opposed by occluding the trachea before opening the pleural cavity, the pressure in the closed airways then being equal to lung recoil pressure.

The transpulmonary pressure ($P_{TP}$, the pressure gradient between airway and pleural space) is the force which opposes elastic recoil and is the force therefore which maintains lung volume. If there is no gas flow $P_{TP}$ balances lung recoil pressure exactly.

The elastic recoil forces in the lungs exert traction on all structures within the lungs, pulling on airway surfaces and maintaining their patency. Lung recoil pressure varies with the volume of the lungs (fig. 1) and there are also important regional variations of recoil pressure within the lungs at any given volume. This latter effect is caused by stresses produced in the lungs which distort them from the shape they would adopt outside the thorax to the shape they must assume within the thorax (Agostoni, 1972). In consequence recoil pressure is smaller and airways narrower in the dependent zones of the lungs than in the upper zones.

### *Airway elasticity*

The elasticity of the airways may be determined by measuring change in length and diameter of bronchial segments in an excised lung at different volumes. Hughes, Hoppin and Mead (1972), using this technique, have shown that the elastic properties of the intrapulmonary airways are similar to those of lung parenchyma. The compliance (a measure of elasticity) of the airways is close to that of the

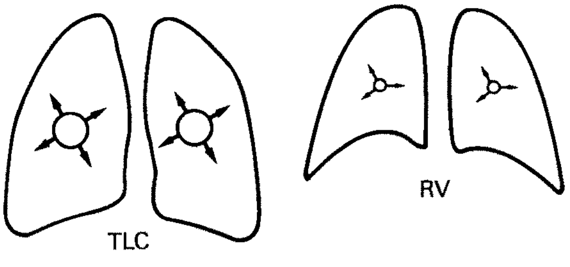

FIG. 1. Diagrammatic representation of the relationship between lung volume and airway size. The arrows represent lung recoil which is large at total lung capacity (TLC) and very small at residual volume (RV).

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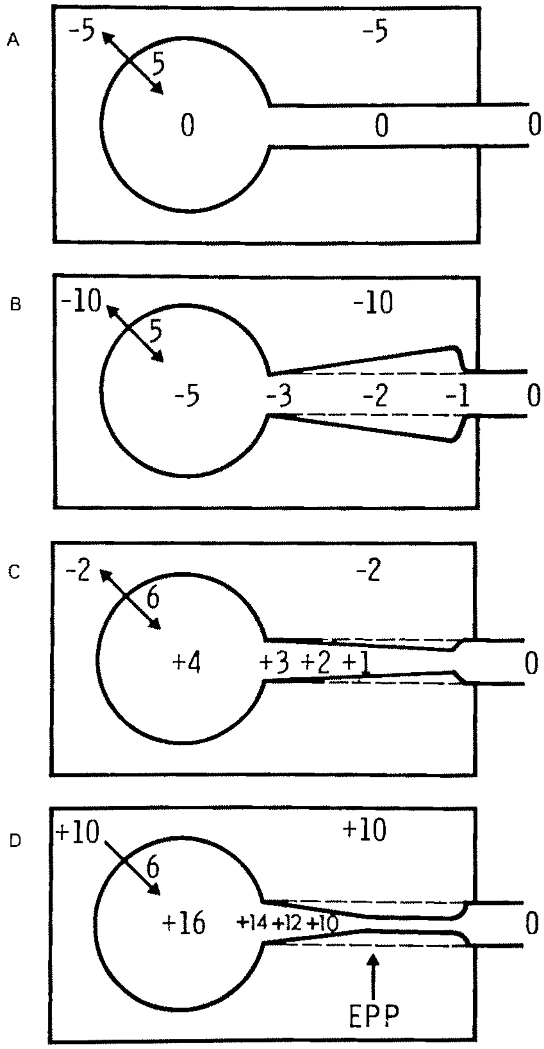
whole lung over the vital capacity range, and this appears to be true both of the bronchi, which have cartilaginous support, and of the peripheral airways (Hughes, Hoppin and Mead, 1972). In consequence, the volume of the airways, containing the anatomical deadspace, is proportional to lung volume and an approximately linear relationship exists between lung recoil pressure and airway volume.

The activity of bronchial smooth muscle adds another element to the relationship between lung volume and airway dimensions. Smooth muscle contraction has the effect of stiffening the airways so that an increase in lung volume produces a smaller increase in airway dimensions and so airway calibre at each lung volume is less than it would be in the absence of bronchomotor activity.



Regional variations in recoil pressure produce regional variations in airway calibre although these have little effect on the distribution of ventilation except at small lung volumes when closure of dependent airways takes place.

### *Effect of gas flow*

When there is no gas flow the same pressure prevails throughout the bronchial tree. The distending force on the airways is the elastic recoil pressure, and *static* airway dimensions are determined by the factors described above (fig. 2A). Gas flow produces a pressure gradient down the airways which depends on the rate and direction of airflow and the resistance offered by the airways. During inspiration the pressure gradient is relatively small because pleural pressure becomes more subatmospheric than it would be under static conditions and there is a slight increase in airway diameter which is greatest in the airways nearest the mouth (fig. 2B). During expiration the pressure gradient is reversed and the airways nearer the mouth become narrower than their static dimensions (fig. 2C). This is called ***dynamic compression*** of the airways and in consequence of this the expiratory resistance exceeds inspiratory resistance at the same lung volume.

FIG. 2. Factors affecting airway diameter. Each box (thorax) contains an alveolus and an intrathoracic airway. A: Static at FRC. The intrapleural pressure (−0.5 kPa, −5 cm $H_2O$) is generated by the elastic recoil pressure. The inside of the alveoli and airways are at atmospheric pressure. A transairway pressure of 0.5 kPa (5 cm $H_2O$) maintains airway patency. B: Early inspiration. The gradient of pressure from alveolus (−0.5 kPa, −5 cm $H_2O$) to pleural space (−1 kPa, −10 cm $H_2O$) causes the alveolus to expand and draw air in through the airways. The resistance of the airway creates a gradient of pressure along the airways so that the transairway pressure gradient is greatest in the airways nearer the mouth. C: Late expiration. Lung elastic recoil pressure is −0.6 kPa (−6 cm $H_2O$) and the resultant transpulmonary gradient of −0.4 kPa (−4 cm $H_2O$) is driving the remainder of the air out of the alveoli. The gradient of pressure between the pleural space and inside of the airways is less than in inspiration and the airways are narrowed, the greatest narrowing occurring at the downstream end. D: Forced expiration. Active contraction of the expiratory muscles has generated a pleural pressure which is greater than atmospheric. Although the pressure in the alveolus still exceeds pleural pressure because of the lung recoil pressure, there is a large gradient of pressure down the airways owing to the high airflow rate. The pleural pressure equals the intraluminal pressure at EPP, the equal pressure point. The pleural pressure exceeds the intraluminal pressure in the downstream portion of the airway which thus closes. This limits the effectiveness of the expiratory muscles and sets a maximal flow rate for each lung volume. Reproduced by kind permission of the Author and Blackwell Scientific Publications Ltd, from Sykes, McNicol and Campbell (1976).

When expiratory airflow is increased, and even with a normal flowrate in patients with pathologically narrowed airways, dynamic compression is increased. The patient may need to produce a pleural pressure which is above atmospheric in order to generate the necessary flowrate and this pressure will compress the airways downstream from the point at which intrabronchial pressure is equal to intrapleural pressure (the equal pressure point—fig. 2D). This mechanism limits the maximum expiratory flow and is said to cause "gas trapping" (Pride, 1971). It should be realized that gas is not permanently trapped by this mechanism because if expiratory effort is maintained long enough the gas will eventually be expired. When the gas flow stops this mechanism ceases, and airway dimensions assume the static dimensions appropriate to that lung volume (fig. 2A). Gas trapping by dynamic airways compression does not, therefore, account for an increase in residual volume, such as occurs in emphysema, as this volume is defined as a static lung volume (Cumming and Semple, 1980) at which there is no gas flow and no pressure gradient within the lumen of the airways.

## METHODS OF ASSESSMENT OF AIRWAY CALIBRE

Airway calibre in man is usually assessed by measurements of gas flowrate under standardized conditions (that is, during forced expiration), or by measurements of both driving pressure ($P$) and gas flow ($\dot{V}$) to obtain the total resistance ($R$) to airflow ($R = P/\dot{V}$). In contrast, an index of regional variations in airway calibre can be derived by measurement of closing volume.

Measurements of flow during forced expiration were introduced by Tiffeneau and Pinelli in 1947, who recorded volume change *v.* time (fig. 3A). More recently an alternative method of analysis, the maximum expiratory flow–volume (MEFV) curve (Hyatt, Schilder and Fry, 1958; Hyatt and Black, 1973), has gained widespread use (fig. 3B).

These tests ignore the force applied by the subject, that is the driving pressure, and it was originally believed that they must, therefore, be inferior to measurements of resistance. It became apparent, however, that the results were usually reproducible because variations in driving pressure only affected the first 20–30% of the expired volume. The explanation for this lies in the mechanism shown in figure 2D. Increasing expiratory effort increases pleural pressure ($P_{PL}$) and this opposes the effects of lung recoil pressure on central airways and tends to compress them. The net result is that an increase in $P_{PL}$ produces an increase in expiratory resistance and this increase is such that, once $P_{PL}$ exceeds central airway pressure, no further increase in expiratory flowrate can occur. Under these conditions expiratory flowrate is largely independent of effort.

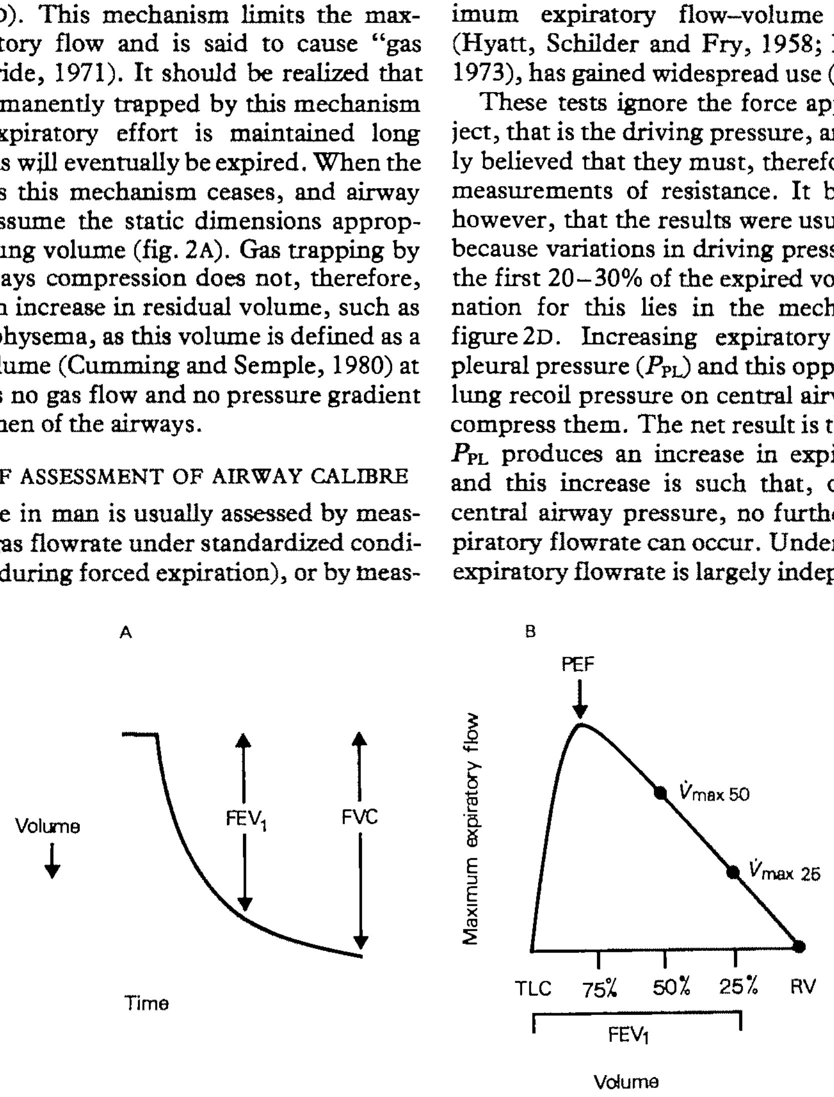


FIG. 3. The two methods of recording the forced expiratory manoeuvre. A: As change in expired volume *v.* time (spirogram) from which are obtained the forced expiratory volume in 1 s (FEV$_1$) and the forced vital capacity (FVC). B: As change in maximum expiratory flowrate *v.* change in volume (MEFV curve). Starting from total lung capacity (TLC), expiratory flow increases to a peak value (PEF) and then declines approximately linearly down to residual volume (RV). Maximum flow when 50% and 25% of the FVC ($\dot{V}_{max\,50}$, $\dot{V}_{max\,25}$) remains to be expired are read from the curve. Reproduced by kind permission of the Author and the Editor of *Br. J. Clin. Pharmacol.*, from Pride (1979).

Three factors govern the flowrate under these conditions:

*Recoil pressure.* The greater the recoil pressure the greater is the change in $P_{PL}$ before flow limitation occurs and thus the greater is the flowrate. In emphysema lung recoil may be greatly diminished and flow limitation may occur under normal resting expiratory flowrates, whereas in pulmonary fibrosis recoil pressure and flow are both increased.

*Bronchomotor tone/bronchial elasticity.* If airways are narrowed by abnormal contraction of bronchial smooth muscle, a greater driving pressure than normal is produced on expiration and $P_{PL}$ reaches values at which flow limitation occurs at lower flowrates than normal.

*Mechanics of the compressed airways.* In the segments of the airways in which flow limitation occurs, gas velocity is very high and this causes a reduction in pressure by the Bernoulli effect, which further collapses the airways. In consequence increasing expiratory effort may produce a reduction in flowrate which is referred to as negative effort dependence. The existence of negative or positive effort dependence or true effort independence under conditions of flow limitation thus depends on the shape of the airway compliance curve in the region of the equal pressure point (Jones, Fraser and Nadel, 1975). As lung volume decreases during expiration the equal pressure point tends to move upstream towards airways that have mechanical properties which produce progressively lower flowrates. Under these conditions measurements reflect *dynamic* airway dimensions and are heavily dependent on pressure gradients produced by air flow.

Measurements made at slower flowrates, similar to those occurring during quiet breathing, reflect airway dimensions which more closely approximate to *static* dimensions. Because flow limitation does not usually occur under these conditions it is necessary to determine the driving pressure and so obtain airways resistance ($R_{AW}$). $R_{AW}$ not only reflects intrapulmonary airway dimensions, but also contains a large component derived from the larynx and upper airway which is a major source of variability. Furthermore, because airflow is not truly laminar, particularly in the upper airway and larynx, resistance increases with increasing flowrate and it is therefore necessary to specify the flowrate at which resistance is measured.

Measurements are usually made to find out about the state of the airways within the lung, and in particular about the state of activity of bronchial smooth muscle. The next section reviews commonly used methods.

### *Peak expiratory flow rate (PEFR)*

This may be measured with a simple variable orifice meter (Wright and McKerrow, 1959; Wright, 1978) and is suitable for general practice and domiciliary use even by unsupervised patients. Peak flow occurs near total lung capacity (fig. 3B) and depends not only on recoil pressure and airway elasticity but is also very dependent on the expiratory effort.

### *Forced expiratory volume in one second ($FEV_1$)*

Measurements of the volume expired in 1 s, and the forced vital capacity (FVC), are commonly made, using a recording spirometer such as the "Vitalograph" (fig. 3A). Usually more than 50% of the $FEV_1$ is expired during the "effort-independent" phase of the forced expiration. Effort-dependence is less than with PEFR and therefore measurements more closely reflect the effects of recoil pressure and airway elasticity. Reduced chest wall or lung compliance, such as in obesity or pulmonary fibrosis, may limit FVC to the point at which $FEV_1$ is reduced even in the absence of airways obstruction and so $FEV_1$ is frequently standardized for FVC by expressing it as the ratio $FEV_1/FVC$.

When measurements are made before and after bronchodilator therapy it is usual to assume that any increase in $FEV_1$ signifies a reduction in bronchomotor tone, rather than an increase in recoil pressure. Airways obstruction reversible by bronchodilator therapy is therefore evidence of hyperreactivity of bronchial smooth muscle (that is, bronchial asthma). While $FEV_1$ measurement assists both in diagnosing asthma and in assessing its severity, it should be noted that reduction in $FEV_1$ is a poor guide to the course of anaesthesia in such patients. In one series 6.5% of symptom-free asthmatic patients developed asthmatic attacks during anaesthesia, while in those with symptoms of asthma, anaesthesia appeared to increase obstruction in 10% and reduce it in 37% (Shnider and Papper, 1961).

In patients with chronic obstructive lung disease the reduction in $FEV_1$ is only slightly, if at all, reversed by bronchodilator therapy. Measurements of $FEV_1$ do not distinguish between obstruction resulting from airway disease and obstruction caused by decreased recoil pressure, although both these may co-exist. Again, $FEV_1$ is a poor guide to the course of anaesthesia, but if it is less than 1 litre then the patient should have blood-gas analysis, and may benefit from chest physiotherapy before and after operation. Arterial carbon dioxide tension is a better guide and those patients who have an increased $Pa_{CO_2}$ are likely to require ventilatory support in the period after surgery (Milledge and Nunn, 1975).

*Maximum expiratory flow–volume curve*

The MEFV curve is usually obtained by measuring flow at the mouth with a pneumotachograph and integrating the flow signal electronically to obtain the change in lung volume. From the curve it is possible to measure PEFR, FVC and $FEV_1$ (if timing marks are displayed on the curve). The combined effects of recoil pressure and bronchomotor tone are inferred from the MEFV curve in the same way as from the $FEV_1$. The shape of the MEFV curve, particularly the effort-independent part of the curve, yields additional information relating to the site and nature of the obstructing lesion. Maximum flow at 50% VC ($\dot{V}_{max\ 50}$) and 25% VC ($\dot{V}_{max\ 25}$) serve to characterize the effort-independent part of the curve (fig. 3B).

In patients with narrowing of the peripheral airways as a result of chronic obstructive lung disease or asthma, the effort-independent part of the curve is usually concave upward (fig. 4A). A localized obstruction in the trachea, such as tracheal stenosis or thyroid compression, produces a characteristic flat-topped curve (fig. 4B) with maximum flowrate over most of the curve being highly effort-dependent. These changes in the shape of the curve reflect differences in the mechanical properties of the flow-limiting segments. The MEFV curve obtained using a helium–oxygen mixture may be compared to that obtained with air. In asthmatic patients little difference is observed as gas flow is limited in the constricted peripheral airways where flow is predominantly laminar. In patients with localized tracheal obstruction flow resistance is markedly density-dependent at higher flowrates. The characteristic shape of the curve is preserved in these patients, but PEFR is increased and this is reflected in the observation that helium–oxygen mixtures are clinically useful in relieving such localized obstruction, while they are of no benefit in asthma.

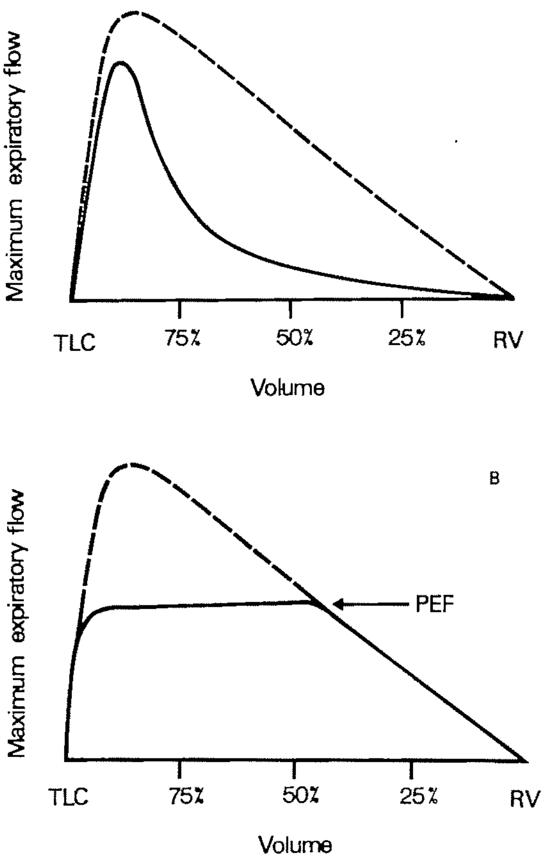


FIG. 4. Typical MEFV curves. A: From a patient with peripheral airways obstruction; B: from a patient with a fixed obstruction in the trachea or upper airway.

*Resistance measurement during normal ventilation*

Resistance may be measured by simultaneously recording gas flowrate at the mouth, volume inspired or expired and transpulmonary or transthoracic pressure. Transthoracic pressure is the difference between mouth pressure and pressure around the thorax and abdomen. Transpulmonary pressure is the pressure difference between the mouth and the outside of the lung, this latter usually being obtained by measuring the pressure in the lower third of the oesophagus using a balloon catheter. The driving pressure is obtained from transpulmonary pressure or transthoracic pressure by subtracting the elastic recoil pressure of the system. Recoil pressure is obtained from the pressure measurements at end-inspiratory and end-expiratory points (that is, points at which there is no gas flow). It is assumed that a linear relationship holds between recoil pressure and lung volume and so driving pressure at intermediate volumes is estimated by subtracting a pressure proportional to volume from the total measured pressure (fig. 5). Resistance is calculated by dividing the driving pressure by the measured flowrate (Otis, Fenn and Rahn, 1950; Mead and Whittenberger, 1953). Depending on the sites at which pressure is measured (transpulmonary or transthoracic), the calculated resistance is pulmonary ($R_L$) or respiratory resistance ($R_{RS}$) (table I). Transthoracic pressure measurements only reflect driving pressure if the lungs are passively inflated and so it is usually used in patients who are paralysed and mechanically ventilated.

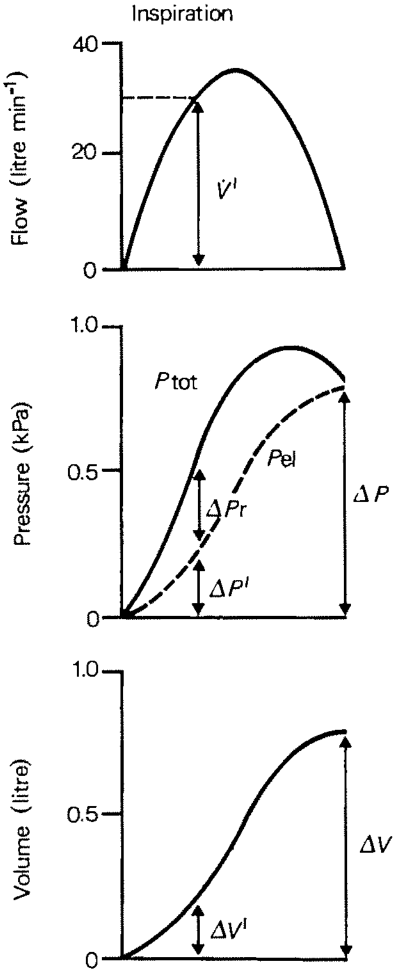


FIG. 5. Pressure, flow and volume recorded during a spontaneous inspiration. Compliance ($\Delta V/\Delta P$) is used to calculate *P*el which is the pressure required to overcome elastic recoil (i.e. proportional to volume change). *P*tot is the total applied pressure (i.e. *P*el plus the pressure required to overcome resistance, $\Delta Pr$). Reproduced by kind permission of the Author and Blackwell Scientific Publications Ltd, from Sykes, McNicol and Campbell (1976).

TABLE I. *Subdivisions of resistance to airflow and their relationship to pressure sampling points. Typical resistance values are shown in parentheses (kPa litre$^{-1}$ s)*

| Pressure sampling point | Resistance obtained (with typical values, kPa litre$^{-1}$ s) | | | |
|---|---|---|---|---|
| Outside thorax | Chest wall (0.08) | | | |
| Pleura | | | | |
| | Lung tissue (0.01) | | | |
| Alveoli | | | | Respiratory (0.23) |
| | Lower airways (0.06) | | Pulmonary (0.13) | |
| Trachea | | Airway (0.12) | | |
| | Upper airway (0.06) | | | |
| Mouth | | | | |

These methods are suitable for use during anaesthesia, and if the trachea can be intubated a major source of variability, the resistance of the larynx and upper airway, can be eliminated. Interpretation of results poses problems, however, as recoil pressure can vary between successive measurements as a result of changes in lung volume associated with anaesthesia. Unless lung volume is measured, and shown not to account for the observed changes in resistance, then the changes in resistance cannot safely be ascribed to changes in bronchomotor tone.

### *Airway resistance using body plethysmography*

If a subject is seated inside an airtight box, and breathes to atmosphere through a port connected to the exterior of the box, then the box pressure changes proportionately to the change in the lung volume. This is because movement of the body surface during respiration displaces a volume of gas equal to the volume displaced by the lung. If the port is sealed and the subject breathes the air within the box, then it might be expected that there would be no pressure changes in the box as the change in trunk volume should exactly equal the volume inspired and expired at the mouth. During gas flow this is not quite the case as the changes of pressure in the alveoli cause compression or expansion of gas in the lungs. This causes a small change in trunk volume which is not balanced by an equal volume displaced at the mouth. For example, if the trunk volume decreases by 52 ml while 50 ml is expelled from the mouth, then 2 ml of gas is lost to the box by gas compression within the lungs. If the actual lung volume is known, then Boyles' Law can be used to calculate alveolar pressure. Thus, in the above example, if lung volume is 2 litre and absolute pressure at the mouth is 100 kPa then:

$$\text{alveolar pressure} = 100 \times 2000/(2000-2) = 100.1\ \text{kPa}$$

Alveolar pressure is 0.1 kPa (1 cm $H_2O$) greater than mouth pressure. If flowrate is measured at the mouth, then airways resistance can be measured (DuBois, Botelho and Comroe, 1956). In practice, box pressure changes are calibrated in terms of alveolar pressure changes, with the subject making respiratory efforts against an occluded airway. Alveolar pressure is obtained by measuring pressure at the mouth as, with the airway occluded, mouth pressure equals alveolar pressure.

Because this method requires the subject to be enclosed in a box and to make active respiratory efforts, it is unsuitable for use during anaesthesia.

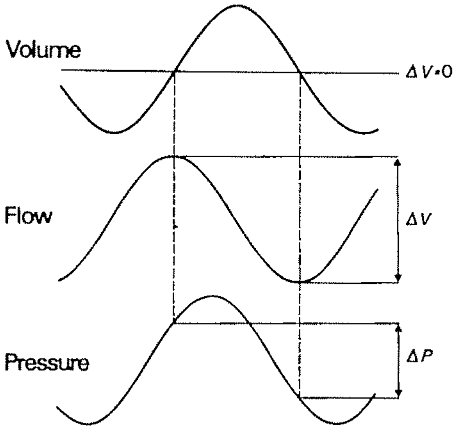


FIG. 6. The relationship between pressure, flow and volume during forced airflow oscillation. Note that lung volume is unchanged ($\Delta V = 0$) at successive instants of peak flow and thus $\Delta P$ is the driving pressure producing this flow ($\Delta \dot{V}$).

*Resistance using the forced oscillation method*

An alternating airflow (typically 50 ml tidal volume at 3 Hz) is applied at the mouth using a loudspeaker or a mechanical pump connected to the breathing circuit. The oscillating flow and pressure are measured at the mouth. The points of peak inspiratory and expiratory flow produced by the oscillations are determined and the pressure difference between successive instants of peak flow is measured. Lung volume is identical at these points and the pressure difference observed is the resistive pressure across the respiratory system at that peak-to-peak flowrate (fig. 6). From these pressure and flow measurements respiratory resistance is obtained (Goldman et al., 1970; Hyatt et al., 1970). The frequency of oscillation should be sufficiently slow in relation to the time constants of the alveoli and their conducting airways so that the distribution of the oscillating airflow is reasonably uniform throughout the lungs. Frequencies up to 10 Hz are satisfactory under normal conditions in subjects with healthy lungs. With less homogenous lungs, a frequency limit of about 3 Hz is desirable if $R_{RS}$ is not to be overestimated. This method is suitable for use in anaesthetized patients, although the problem remains of distinguishing between changes resulting from change in bronchomotor tone and those caused by change in lung volume.

*Measurement of closing volume*

Measurement of closing volume provides information about regional airway calibre. To obtain the closing volume it is necessary to arrange for there to be different concentrations of a tracer gas in the upper and lower zones of the lungs. This may be achieved by inhaling a small volume of an inert tracer gas (such as argon or xenon-133) from residual volume, followed by air to total lung capacity. Because the tracer gas is introduced when dependent airways are closed, its concentration is greatest in the upper zones of the lungs. The patient then slowly exhales and the tracer concentration is measured at the mouth. When the airways in the dependent parts of the lungs begin to close again, the expired gas shows a sudden increase in tracer concentration as a greater fraction of expired gas comes from the upper zones where tracer concentration is greatest. The point at which tracer concentration in the expired air increases above the alveolar plateau signals the onset of airways closure (fig. 7). The volume expired from this point to residual volume is the closing volume of the lungs (Dollfus, Milic-Emili and Bates, 1967).

Closing volume increases with either an increase in bronchomotor tone or a decrease in recoil pressure. However, the presence of lung disease often converts the alveolar plateau into a curve on which there is no clear cut inflection in tracer concentration to enable the closing volume to be measured.

## AIRWAY FUNCTION DURING ANAESTHESIA

Anaesthesia is usually associated with a reduction in functional residual capacity (FRC) and thus with a reduction in both recoil pressure and airway calibre.

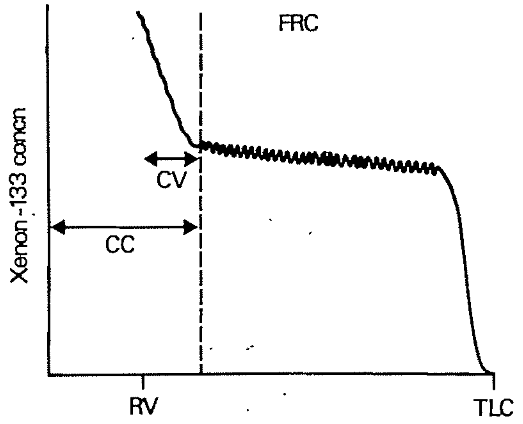


FIG. 7. Closing volume (CV) demonstrated by inhaling a tracer gas (xenon-133) near residual volume. Xenon concentration is measured during the subsequent expiration from TLC. Xenon is absent initially as deadspace gas is expired. Its concentration then increases to reach a plateau (the alveolar plateau). Near RV, xenon concentration again increases abruptly to signal the onset of airways closure.

Different anaesthetic agents may influence the extent of the reduction in lung volume and therefore have differing effects on airway calibre through mechanisms other than change in bronchomotor tone. Under these circumstances resistance measurements must either be repeated at identical lung volumes, or alternatively the way in which resistance varies with lung volume must be accurately established.

Given that gas flow within the lungs is predominantly laminar at low flowrates, it can be shown that the relationship between airways resistance and lung volume is hyperbolic (Jordan et al., 1981) and this relationship has been demonstrated in conscious subjects (Briscoe and DuBois, 1958) and in anaesthetized patients (Lehane, Jordan and Jones, 1980). The effect of a change in bronchomotor tone is a change in the shape of the hyperbolic curve (fig. 8). This change in shape may be quantitated in two closely related ways:

*Specific airways conductance*

From the hyperbolic relationship between resistance and volume it may be expected that the reciprocal of resistance, conductance, should be a linear function of lung volume (fig. 9). Blide, Kerr and Spicer (1964), using a body plethysmograph, and a wide-bore needle to sense tracheal pressure, showed that there was, indeed, a linear relationship between the conductance of the airways in the lung ($G_{LAW}$) and lung volume.

Change in bronchomotor tone affects the slope of this straight line relationship and this provides the basis for the standard plethysmographic method for specific conductance. $R_{AW}$ is measured as described earlier, and its reciprocal, airways conductance ($G_{AW}$) is divided by lung volume (also obtained during the measurement of $R_{AW}$ in the plethysmograph). This ratio is called specific airways conduc-

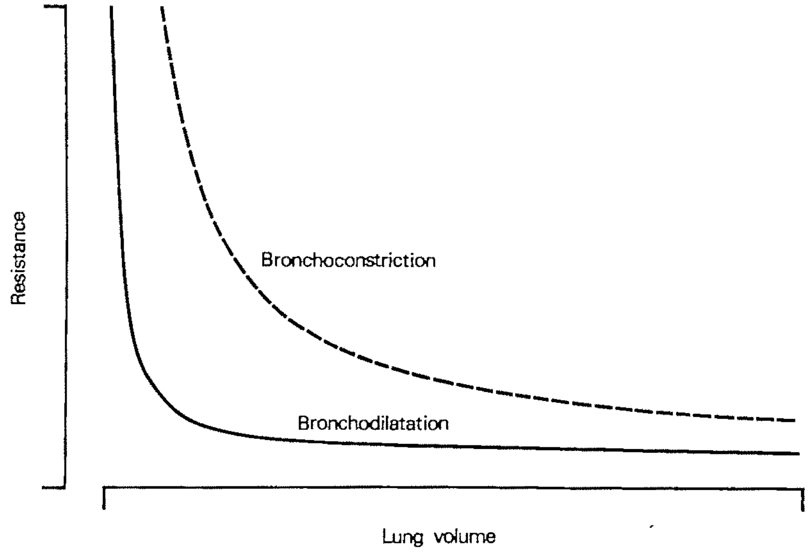


FIG. 8. Diagrammatic representation of the effect of a change in bronchomotor tone on the resistance–volume hyperbola.

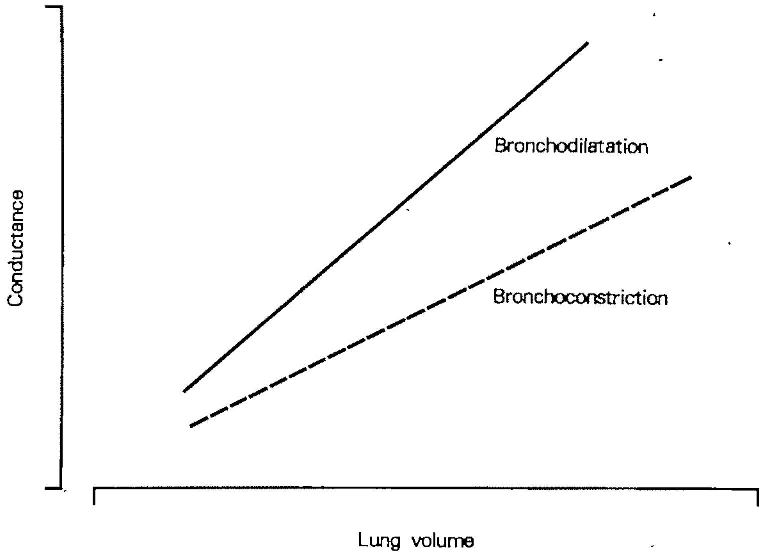


FIG. 9. Diagrammatic representation of the effect of a change in bronchomotor tone on the slope of a conductance–volume plot.

tance (s.$G_{AW}$). Errors are introduced insofar as this ratio represents the slope of the conductance–volume line only if the line passes through the origin of the graph (that is, conductance does not decrease to zero until all gas is expelled from the lungs). This is not the case, however, because conductance reaches zero at a lung volume close to residual volume. Furthermore, inclusion of upper airways conductance renders the relationship nonlinear. In spite of this, variations in s.$G_{AW}$ resulting from change in lung volume are small provided that measurements are not made close to residual volume.

The plethysmographic method is unsuitable for use in mechanically ventilated patients and a different approach, the analysis of the resistance–volume hyperbola must be used.

*Analysis of resistance-volume plots*

We have developed this approach in which $R_{RS}$ is measured continuously using the forced oscillation technique. The lungs are deflated slowly towards residual volume and change in lung volume from FRC is measured by integrating the pneumotachograph signal. A hyberbolic equation is then fitted to the resistance–volume data using computer-aided hyperbolic regression (Jordan et al., 1981).

A simple hyperbolic equation in terms of resistance ($R$) and change in volume ($V_L$) from FRC is as follows:

$$1/R = s.G_{LAW} \times V_L \qquad (1)$$

This is not an adequate model for the data for two reasons. First, some components of resistance are dependent of lung volume (lung tissue, chest wall and upper airway resistance) and these can be included in a more complete equation as the term $R_A$ (equation (2)). Second, all airways would close, so their resistance would be infinite, if the lungs were to be deflated to residual volume. A further term (ERV) representing this volume is also included in equation (2) thus:

$$1/(R - R_A) = s.G_{LAW}(V_L - \text{ERV}) \qquad (2)$$

and this is represented graphically in figure 10. Hyperbolic regression determines the parameters (s.$G_{LAW}$, $R_A$ and ERV) of equation (2) that best fit the resistance–volume data and change in s.$G_{LAW}$ is used as an index of change in bronchomotor tone.

This approach makes it possible to distinguish between the effects of lung volume and bronchomotor tone on $R_{RS}$ in anaesthetized, mechanically ventilated patients. Figure 11 shows the effects of the addition of halothane to the inspired gas mixture in two anaesthetized patients. In both patients this produced a reduction in bronchomotor tone illustrated here by the change in shape of the resistance–volume curves. In patient 8 (fig. 11B) the resistance over the tidal volume range is even further reduced by a concomitant change in lung volume

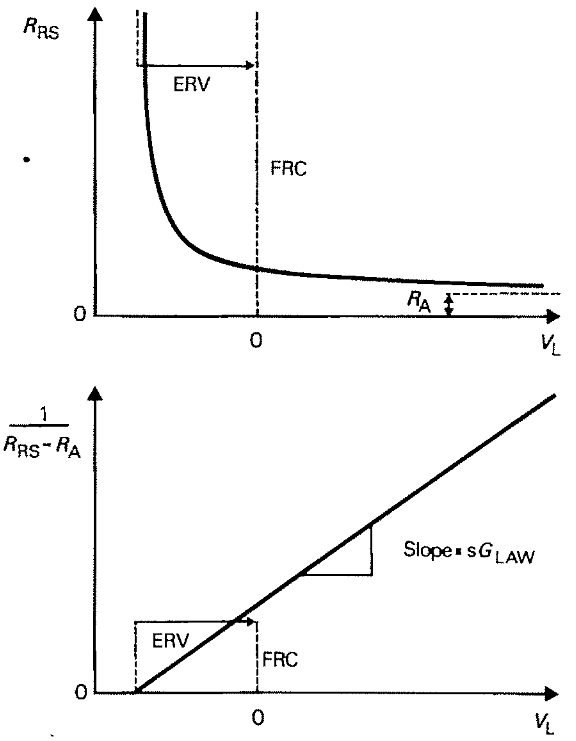


FIG. 10. Diagram of resistance and conductance curves to show $R_A$, ERV and s.$G_{LAW}$ (see text).

which is shown by the increase in ERV. The mechanism of this change is not clear, but may be a result of a reduction in central blood volume caused by peripheral vasodilatation (Lehane, Jordan and Jones, 1980). As ERV may be very small in some anaesthetized patients it can be seen that small changes in lung volume may produce gross changes in $R_{RS}$. The great variability in published data on the effects of anaesthetics on bronchomotor tone is probably a result of failure of workers to allow for the effects of change in lung volume.

## CONCLUSION

Various methods are available for the assessment of airway calibre. For the assessment of patients before operation the simpler tests of forced expiration usually suffice. When more sensitive methods are required, usually for research purposes, then analysis of the maximal expiratory flow–volume curve or plethysmographic determination of specific conductance may be appropriate. With suitably trained subjects the forced oscillation method for s.$G_{LAW}$ is a useful alternative to the plethysmographic method. During anaesthesia and in patients requiring mechanical ventilation on the Intensive Therapy Unit, the forced oscillation method for s.$G_{LAW}$ is probably the only practical method available which

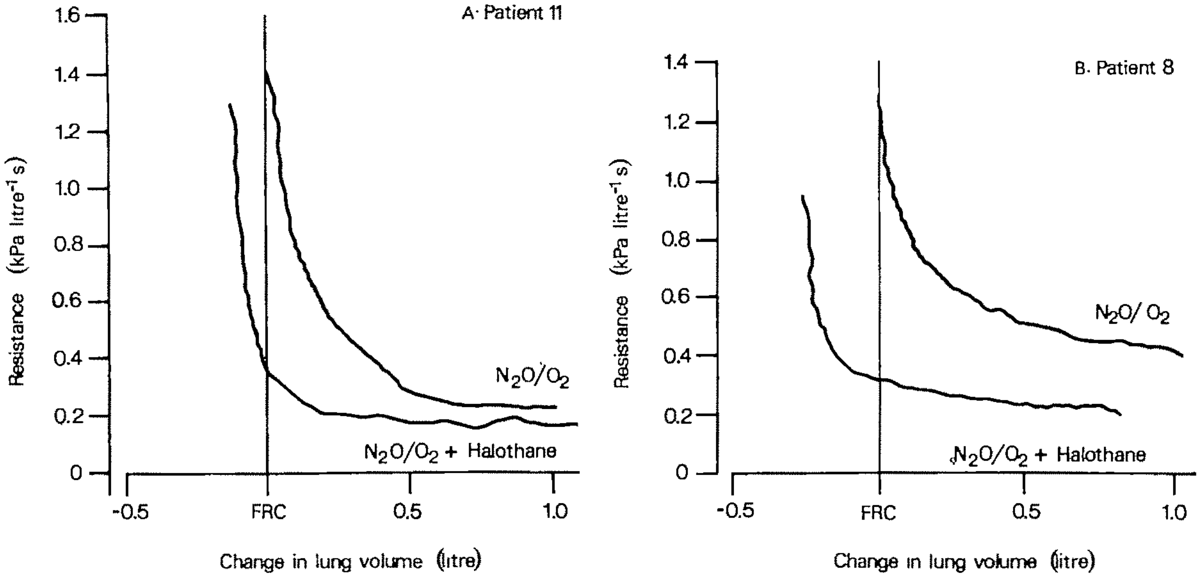


FIG. 11. A: The effect of halothane in one patient to show a small change in ERV and a large change in respiratory resistance. The decrease in resistance over the tidal range is almost entirely a result of reduction in bronchomotor tone. B: A different patient illustrates another mechanism for a decrease in respiratory resistance following addition of halothane. The decrease in resistance is accounted for largely by an increase in ERV, although there is an independent reduction in bronchomotor tone.

yields data on airway calibre which can be reliably interpreted in terms of effects of bronchomotor tone and of recoil pressure.

## REFERENCES

Agostoni, E. (1972). Mechanics of the pleural space. *Physiol. Rev.*, 52, 57.

Blide, R. W., Kerr, D. H., and Spicer, W. S. (1964). Measurement of upper and lower airway resistance and conductance in man. *J. Appl. Physiol.*, 19, 1059.

Briscoe, W. A., and DuBois, A. B. (1958). The relationship between airway resistance, airway conductance and lung volume in subjects of different age and body size. *J. Clin. Invest.*, 37, 1279.

Cumming, G., and Semple, S. J. (1980). *Disorders of the Respiratory System*, 2nd edn, p.37. Oxford: Blackwell.

Dollfus, R. E., Milic-Emili, J., and Bates, D. V. (1967). Regional ventilation of the lung studied with boluses of $^{133}$xenon. *Respir. Physiol.*, 2, 234.

DuBois, A.B., Botelho, S. Y., and Comroe, J. H. (1956). A new method for measuring airway resistance in man using a body plethysmograph: values in normal subjects and in patients with respiratory disease. *J. Clin. Invest.*, 35, 327.

Goldman, M., Knudson, R. J., Mead, J., Peterson, N., Schwaber, J. R., and Wohl, M. E. (1970). A simplified measurement of respiratory resistance by forced oscillation. *J. Appl. Physiol.*, 28, 113.

Hughes, J. M. B., Hoppin, F. G., and Mead, J. (1972). Effect of lung inflation on bronchial length and diameter in excised lungs. *J. Appl. Physiol.*, 32, 25.

Hyatt, R. E., and Black, L. F. (1973). The flow-volume curve: a current perspective. *Am. Rev. Respir. Dis.*, 107, 191.

—— Schilder, D. P., and Fry, D. L. (1958). Relationship between maximum expiratory flow and degree of lung inflation. *J. Appl. Physiol.*, 13, 331.

—— Zimmerman, I. R., Peters, G. M., and Sullivan, W. J. (1970). Direct writeout of total respiratory resistance. *J. Appl. Physiol.*, 28, 675.

Jones, J. G., Fraser, R. B., and Nadel, J. A. (1975). Prediction of maximum expiratory flow rate from area-transmural pressure curve of compressed airway. *J. Appl. Physiol.*, 38, 1002.

Jordan, C., Lehane, J. R., Jones, J. G., Altman, D. G., and Royston, J. P. (1981). Specific conductance using forced airflow oscillation in mechanically ventilated human subjects. *J. Appl. Physiol.*, 51, 715.

Lehane, J. R., Jordan, C., and Jones, J. G. (1980). Influence of halothane and enflurane on respiratory airflow resistance and specific conductance in anaesthetized man. *Br. J. Anaesth.*, 52, 773.

Mead, J., and Whittenberger, J. L. (1953). Physical properties of human lungs measured during spontaneous respiration. *J. Appl. Physiol.*, 5, 779.

Milledge, J. S., and Nunn, J. F. (1975). Criteria for fitness for anaesthesia in patients with chronic obstructive lung disease. *Br. Med. J.*, 3, 670.

Otis, A. B., Fenn, W. O., and Rahn, H. (1950). Mechanics of breathing in man. *J. Appl. Physiol.*, 2, 592.

Pride, N. B. (1971). The assessment of airflow obstruction. Role of measurements of airway resistance and of tests of forced expiration. *Br. J. Dis. Chest*, 65, 135.

——(1979). Assessment of changes in airway calibre. 1. Tests of forced expiration. *Br. J. Clin. Pharmacol.*, 8, 193.

Shnider, S. M., and Papper, E. M. (1961). Anesthesia for the asthmatic patient. *Anesthesiology*, 22, 886.

Sykes, M. K., McNicol, M. W., and Campbell, E. J. M. (1976). *Respiratory Failure*, 2nd edn, p.20. Oxford: Blackwell.

Tiffeneau, R., and Pinelli, A. (1947). Air circulant et air captif dans l'exploration de la fonction ventilatrice pulmonaire. *Paris Méd.*, 37, 624.

Wright, B. M. (1978). A miniature Wright peak-flow meter. *Br. Med. J.*, 2, 1627.

—— McKerrow, C. B. (1959). Maximum forced expiratory flowrate as a measure of ventilatory capacity with a description of a new portable instrument for measuring it. *Br. Med. J.*, 2, 1041.

*Br. J. Anaesth.* (1982), 54, 763

# ASSESSMENT OF THE EFFECTS OF DRUGS ON RESPIRATION

C. JORDAN

Many drugs used in anaesthetic practice such as the opiates, sedatives, barbiturates and volatile anaesthetic agents cause respiratory depression. This often leads to a cautious use of such agents and on occasions this may lead to the administration of a dose of drug which is less than that desired for adequate therapeutic effect. This may often be the case with the administration of opiates for postoperative pain. Consequently, there is a great interest in measuring the respiratory effects of these commonly used drugs both in the laboratory and in the clinical environment, and this interest clearly extends into assessing the efficacy and safety of new compounds and of novel modes of administration of new and conventional agents.

Of prime importance in such studies is the development of suitable methods for assessing the respiratory effects of these drug regimes. The methods must be able not only to quantify the degree of respiratory depression, but also detect alterations in the regulation of breathing which may indicate the *potential* for serious depression to occur. A number of methods are available which fulfil these requirements to varying degrees in different applications. This paper describes and classifies these methods, indicates the applications in which they are most useful and outlines some recent findings.

## MEASUREMENT OF RESTING BREATHING

Ventilation is normally well regulated to ensure blood-gas homeostasis. It is thus of primary importance to investigate the effects of drugs on the regulation of ventilation during resting breathing. Ventilation may be measured or its effectiveness assessed by measurement of blood-gas tensions.

### *Practical measurement of ventilation*

Methods generally involve either (a) direct measurement of ventilation where the subject is required to use a mouthpiece and nose-clip or tight-fitting face mask; or (b) indirect measurements which avoid the use of direct attachment to the airway so as to render breathing more natural, avoid increased deadspace, allow greater subject mobility and facilitate measurements during sleep.

*Direct methods.* Spirometry: the subject breathes into a spirometer (bell, piston or wedge type), with carbon dioxide absorbed if necessary, the change in spirometer volume being recorded. Inaccurate response at high frequencies may cause errors with rapid breathing.

Pneumotachographs: the pressure difference across the pneumotachograph head is proportional to flow. Electronic integration of the flow signal provides a volume signal which may be summed to give minute volume. Errors may be caused by temperature changes and moistening of the pneumotachograph screen by expired gas or alterations in gas composition.

Other direct methods of measurement of ventilation include mechanical flow meters (e.g. dry gas meters), hot-wire anemometers, turbulent flow resistors and ultrasound devices. A full account of methods of direct measurement of ventilation is given by Nunn (1977).

*Indirect methods.* Canopy monitor: the subject's head is enclosed in a rigid canopy with the neck sealed with a foam rubber gasket (Sorkin et al., 1980). The canopy is supplied with a fresh gas flow and is maintained at atmospheric pressure by removing gas at a suitable rate. A pneumotachograph or spirometer attached to the canopy measures ventilatory volumes. Restricted access to the patient may be a disadvantage in pharmacological studies, although the method does facilitate measurement during sleep.

Strain gauges: these are applied around the torso and measure changes in circumference during breathing. The mercury-in-silastic strain gauge is the commonest method, and with multiple gauges and electronic signal processing a reasonable estimation may be obtained of tidal volume and of the volumet-

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ric contributions of the rib cage and abdomen/diaphragm (Faithful, Jones and Jordan, 1979). The accuracy of these devices is limited because changes in shape of the torso alter the relationship between circumference and volume. Such shape changes may occur at the extremes of lung volumes, when the work of breathing is increased or when changing position.

Electrical impedance pneumography: changes in electrical impedance of the thorax that occur during breathing are measured. The accuracy of this technique is reported to be somewhat limited, especially when changing position (Ashutosh et al., 1974), and it is not clear whether the measurements relate to change in thoracic circumference or volume.

Magnetometry: a coil placed on one body surface generates an electromagnetic field that is sensed by another coil on an opposite surface (Mead et al., 1967). Pairs of coils on the rib cage and abdomen are generally used to measure anteroposterior diameters which are then related to volume changes. Changes in shape of the torso under certain circumstances can produce large errors in volume estimations, although use of multiple magnetometers may overcome this difficulty by enabling suitable calculations of cross-sectional areas.

Respiratory inductive plethysmography: two zigzag coils of insulated wire attached to highly compliant belts are worn around the rib cage and abdomen. Changes in cross-sectional area of the thoracic or abdominal coil region produce proportional changes in coil self-inductance, which is thus related to change in volume of the appropriate region. Since the transducer measures cross-sectional area directly, virtually independent of shape, the accuracy of volume measurement is little affected by distortion of the thorax or abdomen and a single calibration is valid over a wide range of changes in body position (Cohn et al., 1978; Watson, 1980). This method is therefore highly suited to long-term monitoring and the author and his colleagues have successfully applied it to testing the respiratory effects of drugs (Catling et al., 1980; Jordan, Jones and Pinto, 1980; Royston, Jordan and Jones, 1981). Excessive body movements can produce artefacts in the respiratory signal and care should be taken to ensure that the belts remain in place.

Other indirect methods of measurement of ventilation include body plethysmography (Johnson and Mead, 1963) and the pressure capsule (Wright and Callan, 1980). A thorough review of methods for monitoring ventilation without a physical connection to the airway has been presented by Sackner (1980).

*Practical measurement of blood-gas tensions*

*Direct methods.* Arterial blood samples: sampling of arterial blood and subsequent blood-gas analysis enables $P\text{O}_2$, $P\text{CO}_2$ and pH to be measured directly. Repeated arterial punctures or arterial catheterization may be considered unethical procedures for the assessment of drugs in normal subjects and most patients. "Spot" samples may miss transient changes in breathing and the action of taking a sample can disturb the pattern of breathing.

Sampling of arterialized blood: arterialized capillary or superficial venous blood may be sampled to obtain an index of arterial blood-gas tensions. Changes in peripheral circulation may occur as a result of drug administration thereby altering the relationship between peripheral and arterial blood-gas tensions.

*Indirect methods.* Transcutaneous methods: diffusion of oxygen and carbon dioxide through the skin enables the measurement of $P\text{O}_2$ and $P\text{CO}_2$ using special electrodes, mass spectrometry or infra-red absorption analysis. The instruments may require initial calibration by checking the subject's arterial blood-gas tensions and the accuracy of measurements can be impaired by changes in skin blood flow and metabolism. Response times are usually of the order of minutes.

End-tidal carbon dioxide sampling: sampling of the end-tidal $P\text{CO}_2$ is a convenient means of estimating $P\text{CO}_2$ in arterial blood and is reasonably accurate in patients with normal lungs. Changes in arterial $P\text{CO}_2$ may therefore be estimated on a breath-by-breath basis by continuous sampling of expired gas with a rapidly resppnding infra-red carbon dioxide analyser or respiratory mass spectrometer. The relationship between end-tidal $P\text{CO}_2$ and arterial $P\text{CO}_2$ can be altered by large changes in respiratory rate or tidal volume.

End-tidal oxygen sampling: the mass spectrometer or fuel cell (Weil, Sodal and Speck, 1967) may be used to sample end-tidal $P\text{O}_2$. End-tidal $P\text{O}_2$ is not a reliable index of arterial $P\text{O}_2$ because of large and variable alveolar–arterial $P\text{O}_2$ differences.

Ear oximetry: a non-invasive estimation of arterial blood oxygen saturation using ear oximetry is convenient and reasonably accurate. Automatic computations from absorbance of eight different wavelengths of light enable allowances to be made for ear blood volume, skin thickness and pigmentation. The Hewlett–Packard ear oximeter (HP 47201A) uses this approach and has been shown to provide good accuracy of oxygen saturation measurement over the range 60–99% (Saunders, Powles and Rebuck, 1976) and to have a time constant of approximately 3 s (Douglas et al., 1979).

### *Interpretation of measurements of ventilation and blood-gas tensions*

Many pharmacological agents alter oxygen consumption and it is important to remember that minute volume may change in response to metabolic requirements. For example Jennett, Barker and Forrest (1968) found that morphine 10 mg depressed resting ventilation by 20% but also reduced oxygen consumption by 23%. Further, Santiago and colleagues (1979) found that ventilation at different levels of exercise was significantly reduced after morphine 14 mg, but that oxygen consumption during exercise was similarly reduced so that the relationship between ventilation and metabolic rate was not altered. Decreased ventilation does not therefore necessarily indicate that ventilation is depressed and blood-gas estimations are crucial in interpreting changes in ventilation in relation to metabolic requirements. Adequacy of ventilation may be assessed from measurements of arterial $P\text{CO}_2$, an increase in $P\text{CO}_2$ implying that alveolar ventilation has diminished in relation to carbon dioxide production. Sequential sampling of arterial $P\text{CO}_2$ before and after the administration of a drug enables quantitation to be made of the magnitude and time course of any change in ventilation in relation to metabolic requirements.

Measurements of arterial $P\text{O}_2$ are generally considered less useful in assessing the effects of drugs on the control of ventilation, since the variable alveolar–arterial $P\text{O}_2$ difference reflects the efficiency of gas exchange and is mainly dependent on the relative distribution of pulmonary ventilation and perfusion.

In addition to the effects on minute volume and blood-gas tensions, respiratory depressant drugs often produce marked changes in breathing pattern. The normal regular breathing pattern may become irregular, with variable tidal volumes and occasional apnoeic episodes or sometimes a Cheynes–Stokes pattern with tidal volume waxing and waning. This type of change may be quite pronounced even when overall ventilatory depression is minimal: for example striking changes in breathing pattern were reported after phenoperidine and morphine even though end-tidal $P\text{CO}_2$ was only increased by 0.25–0.4 kPa (Jennett, Barker and Forrest, 1968). It is therefore desirable to include continuous measurements of ventilation in the assessment of drugs, especially as such disturbed breathing patterns may represent part of a continuous spectrum of response with at one extreme excessively long apnoeas and dangerous hypoventilation.

Minute volume ($\dot{V}$) represents the temporal summation of a series of individual breaths, but it is often more informative to interpret changes in minute volume in terms of the average breath. Each breath may be subdivided into tidal volume ($V_T$) and timing components (inspiratory and expiratory times $T_I$ and $T_E$, total breath time $T_{tot}$) (Milic-Emili and Grunstein, 1976; Remmers, 1976; Milic-Emili and Aubier, 1980). We may derive

$$\dot{V} = V_T \times f = V_T/T_{tot} = (V_T/T_I) \times (T_I/T_{tot})$$

where $f$ = respiratory rate. $V_T/T_I$ may be considered to represent inspiratory drive and $T_I/T_{tot}$ to represent the proportion of time taken up by inspiration, or the inspiratory duty cycle (fig. 1). This separation of breathing into drive and timing elements enables changes in pulmonary ventilation to be interpreted as alterations in either or both components (see below and figure 7) and may enable sites of actions of drugs to be localized.

### *Problems and precautions*

Resting ventilation is readily altered by a variety of stimuli. Care is needed to eliminate such stimuli in order to reduce variability in measurements and avoid misinterpretation of drug effects. Subjects should be well informed about the nature of the tests and procedures. They should have adequate prac-

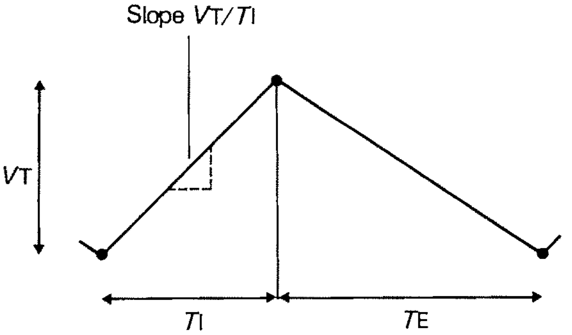

FIG. 1. Schematic illustration of an average respiratory cycle with tidal volume ($V_T$), inspiratory time ($T_I$), expiratory time ($T_E$) and mean inspiratory flow rate ($V_T/T_I$).

tice runs well before the time of the experiment to familiarize them with the procedure and to relieve anxiety which is a major cause of hyperventilation. In addition, the following factors should be considered.

Ingested stimulants: avoid coffee, tea, alcohol, food or drugs before testing.

Diurnal variations: choose the same time of day for crossover studies.

Rest period: subjects should rest for at least 30 min before start of measurements.

Discomfort: avoid unconfortable mouthpieces and nose-clips, poor positioning of breathing equipment, uncomfortable chair or bed, too hot or cold environment, full bladder.

Breathing circuit deadspace and resistance: keep as low as possible and avoid "sticky" valves.

Noises or activity in laboratory: avoid excessive talking or whispering, surround subject with screens and have subjects wear headphones.

Injections or blood samples: keep to a minimum and preferably use indwelling narrow gauge cannulae.

Sleep: significantly alters breathing so should be avoided during study unless specifically wishing to assess sleep–drug interaction.

*Examples of effect of drugs on resting breathing*

Although many studies have included measurements of minute volume and report decreases with respiratory depressant drugs such as morphine (Jennett, Barker and Forrest, 1968; Santiago et al., 1979), most emphasis is usually placed on changes in $P\text{CO}_2$ as this provides an indication of the change in ventilation in relation to metabolic requirements. The measurement of changes in end-tidal $P\text{CO}_2$ during resting breathing has been shown to be a direct test of respiratory depression which is repeatable and sensitive (Jennett, Barker and Forrest, 1968; Engineer and Jennett, 1972). In a comparison of the respiratory effects of drugs administered in equianalgesic doses to normal volunteers (Jordan et al., 1979), the consistency of measurements of end-tidal $P\text{CO}_2$ were such that the magnitude of effect of the drugs was shown to differ significantly in the order meptazinol < morphine < pentazocine (mean increases in end-tidal $P\text{CO}_2$ 0.22, 0.41 and 0.59 kPa respectively). Morphine 7.5–14 mg has been reported to produce increases in end-tidal $P\text{CO}_2$ of 0.33–0.7 kPa in normal volunteers (Jennett, Barker and Forrest, 1968; Weil et al., 1975; Jordan et al., 1979; Santiago et al., 1979; Rigg and Rondi, 1981).

Nitrous oxide administered in analgesic concentrations (20% and 40%) to normal volunteers was found to decrease end-tidal $P\text{CO}_2$ predominantly through an increase in respiratory rate (Royston, personal communication). In the same study, using respiratory inductive plethysmograph coils around thorax and abdomen, it was shown that nitrous oxide diminished the rib cage contribution to tidal breathing (Royston, Jordan and Jones, 1981). A similar finding was made by Rigg and Rondi (1981) using magnetometers to study the effects of morphine on chest wall movement, suggesting that the rib cage contribution to breathing may be highly susceptible to the effects of central depressant drugs. These authors argued that this finding may have practical implications in that morphine may be a special hazard for patients who are dependent on increased intercostal or accessory muscle activity to maintain adequate ventilation. Patients with hyperinflation as a result of chronic obstructive lung disease or patients with increased abdominal respiratory loading as a consequence of obesity or abdominal surgical procedures may therefore be particularly susceptible to the effects of morphine or other central depressant drugs.

As may be anticipated, most volatile anaesthetic agents decrease ventilation and increase resting arterial or end-tidal $P\text{CO}_2$ in proportion to the concentration that is administered (Munson et al., 1966). It is notable that the administration of respiratory depressant drugs to anaesthetized patients is associated with a greater degree of respiratory depression than would be predicted from their effect on $P\text{CO}_2$ and ventilation in conscious volunteers (Potter and Payne, 1970). For example, in one study (Hunter, 1967) respiratory arrest occurred in three of 13 patients given diazepam 2.5–10 mg during anaesthesia with nitrous oxide, oxygen and halothane, whereas the effect of diazepam 15 mg on resting end-tidal $P\text{CO}_2$ in normal volunteers was to produce only a small increase of 0.2 kPa (Jordan, Lehane and Jones, 1980).

Using magnetometers, Tusiewicz, Bryan and Froese, (1977) showed that halothane anaesthesia considerably diminished the rib cage contribution during quiet breathing, a finding supported by Jones and colleagues (1979) using mercury-in-silastic strain gauges. It was concluded that a major part of the depression of ventilation associated with halothane resulted from suppression of intercostal muscle function. Subsequent lack of recruitment of rib cage activity with increased chemical drive, and loss of active stabilization of the rib cage by intercostal muscle contraction resulted at times in paradoxical inward movement of the rib cage during inspiration. Such effects suggest that patients who are normally dependent on intercostal muscle activity may be more prone to hypoventilation while breathing spontaneously during halothane anaesthesia (Tusiewicz, Bryan and Froese, 1977). The suppression of rib cage activity by halothane, together with the central depressant effect on the ventilatory response to carbon dioxide (Ngai, Katz and Farhie, 1965; Munson et al., 1966), explain the quite profound effects of halothane anaesthesia on ventilation.

## TESTS OF CHEMOSENSITIVITY: RESPONSE TO HYPERCAPNIA

In normal man a highly sensitive control mechanism regulates arterial carbon dioxide tension within narrow limits, despite widely varying carbon dioxide production rates. Increases in carbon dioxide tension in arterial blood stimulate the peripheral arterial chemoreceptors directly and the central chemoreceptors in the brain indirectly through concomittant changes in brain extracellular pH. The respiratory centres situated in the pons and medulla respond to the information from the chemoreceptors and maintain arterial $PCO_2$ relatively constant by regulating ventilation. Drugs may well operate at one or more sites in this process although the difficulty in distinguishing between the individual components of the response to carbon dioxide has meant that most drug studies have dealt with the response of the system as a whole. Several techniques have been used to assess the ventilatory response to carbon dioxide, and they may be subdivided into either steady-state or nonsteady-state methods.

### *Steady-state methods*

The steady-state method is the classical approach for assessing the effect of inhaled carbon dioxide on ventilation. The subject breathes various fixed concentrations of carbon dioxide (e.g. 3, 5, 6 and 7%) for periods of about 20 min to allow time for arterial blood and brain extracellular carbon dioxide and hydrogen ion concentrations to approach a steady state. Towards the end of this period the alveolar $PCO_2$ (or preferably arterial $PCO_2$) is measured together with the response to this stimulus which is usually the ventilatory minute volume. If $PCO_2$ is plotted against minute volume, an almost linear relationship is found, the slope of which ($S$) represents the sensitivity of the ventilatory response to carbon dioxide, expressed as the change in ventilation per unit change in $PCO_2$. The intercept of the line with the zero ventilation axis, obtained by extrapolation, may also be measured.

Hypoxia increases the ventilatory response to hypercapnia and so in order to examine the response to carbon dioxide alone, hyperoxic conditions should be used (arterial $PO_2$ greater than 20 kPa). Useful information can be obtained by repeating the steady-state procedure at progressively lower arterial oxygen tensions (e.g. 13.3 kPa, 6.7 kPa) and plotting $PCO_2$ against minute volume for each oxygen tension (fig. 2). This is the classical way to assess the interaction between carbon dioxide and hypoxia (Lloyd, Jukes and Cunningham, 1958). One of the practical problems of the test, which has been extensively reviewed by Cunningham (1974), is that it is extremely time-consuming. Merely to plot one response line may take an hour and this is clearly a limitation of its usefulness in testing the effects of drugs. A further limitation is that long periods of hypercapnia and possibly hypoxia may alter the absorption, distribution or metabolism, of drugs (Dempsey, 1976). Severinghaus (1976) has proposed a more rapid pseudo steady-state method for determining the ventilatory response to hypoxia and hypercapnia and this may be appropriate for drug studies.

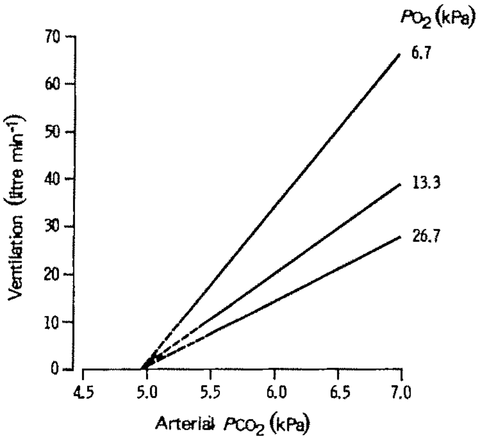

FIG. 2. The effect of oxygen tension on the ventilatory response to hypercapnia. Each line was obtained by breathing different concentrations of carbon dioxide at fixed arterial oxygen tensions (as indicated) and plotting carbon dioxide tension against minute volume. The slope of each line ($S$) represents the sensitivity of the ventilatory response to carbon dioxide at the oxygen tension.

### *Nonsteady-state methods*

*Rebreathing techniques*

These techniques, which involve generating a progressively increasing carbon dioxide stimulus, have become routine in many laboratories largely as a result of their convenience and speed. The rebreathing techniques described by Read (1967) is generally used and involves the subject rebreathing from a small bag containing carbon dioxide with an initial concentration at or slightly above the mixed venous carbon dioxide concentration. The bag is usually primed with a volume approximately equal to the subject's vital capacity plus 1 litre and the mixture is usually hyperoxic (e.g. 7% carbon dioxide, 50% oxygen, balance nitrogen). After 30–60 s of rebreathing, the $P\text{CO}_2$ in the bag equilibrates with alveolar gas and arterial and mixed venous blood so that $P\text{CO}_2$ at these locations, and presumably at the chemoreceptor sites, changes at the same rate. Carbon dioxide tension increases steadily with time at a rate of approximately 0.4–0.8 kPa $\text{min}^{-1}$ and this produces a steadily increasing stimulus to ventilation. Oxygen tension, although decreasing progressively, is maintained greater than 20 kPa throughout the rebreathing period (usually about 4–6 min). To ensure hyperoxia at the start of rebreathing, the subject usually breathes 50% oxygen for several minutes beforehand.

Carbon dioxide tension measured in the rebreathing gas mixture defines the stimulus to breathing since it is in equilibrium with arterial and mixed venous blood and it is therefore unnecessary to take arterial blood samples. As in the steady state test, a virtually linear relationship between minute volume and $P\text{CO}_2$ is normally found, although non-linearity is often seen at lower $P\text{CO}_2$ (hockey stick appearance) and the line is shifted to the right of the steady-state response. There is no significant difference between the slopes of the ventilatory response as assessed by steady state or rebreathing methods in the absence of metabolic alkalosis or acidosis (Read, 1967), although differences between the two methods have been observed in subjects with chronic acid–base disturbances (Linton et al., 1973).

*Practical aspects.* The rebreathing method in its simplest form requires a relatively modest outlay in equipment. Rebuck (1976) has described "...in cookbook style, the ingredients of the rebreathing circuit, along with the operating instructions." Basically, such a system uses a rebreathing bag enclosed in a rigid, airtight container which is connected to a volume measuring device such as a dry gas meter. With this arrangement, often referred to as a "bag-in-bottle", the subject breathes to-and-fro from the bag causing room air to leave and enter the container through the volume measuring device. Alternatively, the rebreathing bag may be replaced by a spirometer filled to the required volume (Jordan, 1981). End-tidal $P\text{CO}_2$ is measured close to the mouth with a rapidly responding carbon dioxide analyser and the sampled gas should preferably be returned to the rebreathing bag. A carbon dioxide response line may be obtained by plotting mean ventilation *v.* end-tidal $P\text{CO}_2$ calculated over successive 30-s intervals during rebreathing. The first point should be calculated during the first 30-s interval following equilibration between $P\text{CO}_2$ in the bag and the lungs as indicated by a steady "mixed venous plateau" in end-tidal $P\text{CO}_2$. The slope and intercept of the ventilatory response line may then be calculated by least squares linear regression. Automatic methods may be used to produce breath-by-breath plots of "instantaneous" minute volume (tidal volume $\times 60/T_{\text{tot}}$) against end-tidal $P\text{CO}_2$ and this considerably simplifies data analysis (Milledge, Minty and Duncalf, 1974).

*Special precautions.* Despite the fact that the rebreathing method is technically straightforward, many workers have encountered problems in producing reliable and reproducible results. All of the problems and precautions stated above in assessing ventilation and blood-gases are particularly relevant to rebreathing experiments. Further precautions include the following. The subject should breathe 50% oxygen in nitrogen through the mouthpiece for 5 min before testing and only be connected (via a wide-bore tap) to the rebreathing circuit when end-tidal $P\text{CO}_2$ is stable ($\pm 0.2$ kPa). The airflow resistance of the rebreathing circuit should be low (e.g. $<0.25$ kPa $\text{litre}^{-1}$ s at 2 litre $\text{s}^{-1}$) and if a non-rebreathing valve is used it should be free from sticking. Rebreathing tests should not be repeated more frequently than once every 15 min. Body temperature has been shown to affect the ventilatory response to carbon dioxide (Cunningham and O'Riordan, 1957) and should be recorded and controlled if necessary by use of blankets or cooling fans. There is wide variability in the slope of the ventilatory response to carbon dioxide between individuals and therefore it is advantageous for subjects in drug trials to act as their own controls. Day-to-day variability within individuals is also large, but may be reduced by ensuring measurements are made at the same time of day at a set time (e.g. 2 h) after a light meal and after 30 min rest in the laboratory. Although variability in measurements within days is smaller than that between days (Sahn et al., 1977) it is advantageous to make duplicate or triplicate measurements and to follow the time-course of a possible drug effect by making measurements serially rather than simply pre- and post-drug. The distribution of slopes of the ventilatory response to carbon dioxide in the population is log-normally skewed (Irsigler, 1976; Mustchin, 1977) and the effects of drugs on slopes appears to be related to initial values, so it is preferable to perform statistical tests on slope data after taking logarithms.

*"Mouth occlusion pressure" response to carbon dioxide rebreathing.* The ventilatory response to carbon dioxide normally represents the overall sensitivity of the respiratory centre to the carbon dioxide stimulus. However, there are circumstances in which the response of the respiratory centre may be unchanged but the ventilatory response to carbon dioxide may be reduced, for example when there are increased mechanical loads to breathing as in patients with obstructive lung disease. In order to obtain more direct measures of respiratory centre output, techniques have been developed which involve recording integrated phrenic nerve activity (Eldridge, 1975) and measurement of the diaphragmatic electromyogram (Lopata et al., 1978). These methods are technically difficult and not easily applied in patients. However, good correlation has been shown between the integrated diaphragmatic electromyogram and the airway pressure developed shortly after the start of inspiration against a transiently occluded airway (Eldridge, 1975; Lopata, Evanich and Lourenço, 1977). This technically simple and non-invasive measurement, usually referred to as "mouth occlusion pressure", is not affected by resistance or compliance of the respiratory system since there is no airflow and no change in lung volume during the occlusion. Mouth occlusion pressure increases linearly with carbon dioxide tension, as does the electromyographic activity of the diaphragm (Altose et al., 1976; Zubillaga et al., 1976), and its rate of increase with carbon dioxide may be used as a more direct measure of the response of the chemoreceptors and respiratory centre. It may therefore be a useful method in drug assessment when the mechanical properties of the lung or chest wall, or both, are likely to alter or in studying patients with obstructive lung disease.

*Special precautions.* It is necessary to measure the airway pressure soon after the commencement of inspiratory effort to avoid conscious responses and volume-related reflexes. Several groups measure the pressure at 100 ms ($P_{0.1}$) after the start of inspiratory effort (Whitelaw, Derenne and Milic-Emili, 1975; Altose et al., 1976; Jordan, 1981), although a survey of various times of sampling suggested that 175–200 ms provides more reproducible data (Yoshida et al., 1981). Brief occlusions are difficult to produce with manually operated valves and so an automatic method has been developed in which a solenoid valve occludes the airway briefly (for 120 ms) at the start of inspiration on selected breaths during a carbon dioxide rebreathing procedure (Jordan, 1981). The subatmospheric pressure generated in the airway may be displayed (fig. 3) and the pressure at 100 ms sampled and plotted automatically against end-tidal carbon dioxide tension (fig. 4). The ventilatory response to carbon dioxide may be assessed simultaneously with the $P_{0.1}$ response since the brief occlusions do not perturb ventilation.

In studies on the effects of drugs on the mouth occlusion pressure response to carbon dioxide, it is necessary to take into account the effects of any changes in functional residual capacity as these may influence the force of inspiratory muscle contraction for a given neuronal drive (Shaffer et al., 1977). The plot of occlusion pressure with time is not always linear (Whitelaw, Derenne and Milic-Emili, 1975; Kryger, Yacoub and Anthonisen, 1975) and could alter its shape with drugs and this should be considered before extrapolating from changes in measurements made early in inspiration.

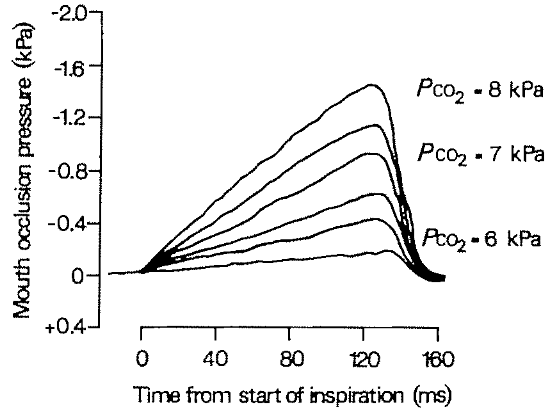

FIG. 3. Superimposed tracings of mouth occlusion pressure plotted against time as carbon dioxide tension increases during a rebreathing procedure. From Jordan (1981) by permission of the Editor of *Medical and Biological Engineering and Computing.*

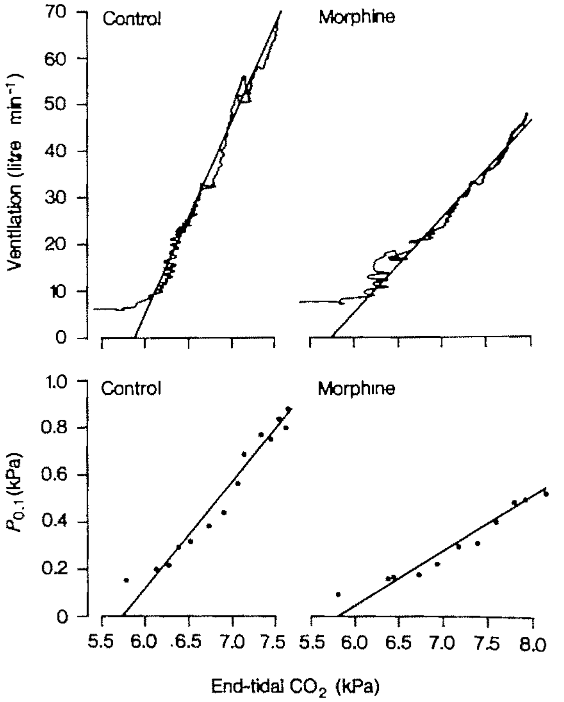

FIG. 4. The effect of morphine on ventilatory and $P_{0.1}$ responses to carbon dioxide in one subject. The two control plots were measured simultaneously 15 min before morphine was given. The plots after morphine were measured simultaneously 75 min following the i.m. injection (10 mg). From Jordan (1981) by permission of the Editor of *Medical and Biological Engineering and Computing*.

### *Tests of transient responses to carbon dioxide*

These non-steady state methods have been developed to quantitate non-invasively the sensitivity and speed of response of the peripheral and central chemoreceptors. A single vital capacity breath of 15% carbon dioxide produces a brief increase in ventilation which is readily detectable (Gabel, Kronenberg and Severinghaus, 1973). If the inhaled carbon dioxide is reduced, then the ventilatory responses are comparable to the spontaneous changes that occur during normal breathing. To increase the resolution of the response, the tests may be carried out while the subject breathes a hypoxic gas mixture or alternatively the response to a large number of tests may be averaged. Ward and Cunningham (1977) used alternate-breath inhalation of carbon dioxide and averaged the response over many breaths. Sohrab and Yamashiro (1980) applied step changes in carbon dioxide concentration between 0 and 6–8% on a breath-by-breath basis in a random sequence determined by a pseudorandom binary sequence generator. Cross-correlation analysis of this input with the ventilatory response yielded estimates of impulse responses and an indirect estimation of peripheral chemoreceptor sensitivity to carbon dioxide and lung to chemoreceptor time lag. Although tests of the transient response to carbon dioxide have the advantage of rapidity and are unaffected by secondary adaptive responses, the technical complexity involved in producing good resolution and reproducibility of response has so far led to relatively little exploitation of such tests in testing the effects of drugs.

### *Examples of the effects of drugs on the response to carbon dioxide*

*Ventilatory response to carbon dioxide.* The rebreathing technique has been fairly extensively applied in assessing the effects of drugs on the ventilatory response to carbon dioxide. Some reported results are summarized in table I.

It has been shown that increasing concentrations of most volatile anaesthetic agents produce increasing depression of the slope of the ventilatory response to carbon dioxide together with a shift in intercept to the right (Larson et al., 1969). Knill and Gelb (1978) showed that 1.1 and 2 MAC concentrations of halothane produced a dose-related depression of the slope of the ventilatory response to carbon dioxide, although 0.1 MAC had no effect. In similar experiments, enflurane was shown to pro-

TABLE I. *Some reported results of the effects of drugs on the ventilatory response to carbon dioxide*

| Drug (source) | Reduction in slope of ventilatory response to carbon dioxide (%) |
|---|---|
| Morphine 7.5–10 mg i.m.<br>(Jennett, Barker and Forrest, 1968; Weil et al., 1975; Jordan et al., 1979; Rigg and Rondi, 1981) | 30–40 |
| Pethidine 75 mg i.m.<br>(Engineer and Jennett, 1972) | 50 |
| Pentazocine 45–60 mg i.m.<br>(Engineer and Jennett, 1972; Jordan et al., 1979) | 33–36 |
| Meptazinol 100 mg i.m.<br>(Jordan et al., 1979) | 7 |
| Diazepam 14 mg i.m.<br>(Jordan, Lehane and Jones, 1980) | 50 |

duce dose-related depression of the carbon dioxide response slope with a significant depression at 0.1 MAC (Knill, Manninen and Clement, 1979). Tusiewicz, Bryan and Froese (1977) studied the relative contributions of rib cage and diaphragm to ventilation during carbon dioxide rebreathing and showed that halothane virtually abolished the increase in rib cage contribution which is normally seen during rebreathing (Pengelly, Tarshis and Rebuck, 1979).

*Mouth occlusion pressure response to carbon dioxide.* Morphine 10 mg was shown to depress the slope of the $P_{0.1}$ response to carbon dioxide by approximately 35%, with good correlation between the slopes of the ventilatory and $P_{0.1}$ responses to carbon dioxide, which was the expected result in normal subjects with no pulmonary mechanical impairment (Jordan, 1981) (fig. 4). Diazepam was shown to depress the $P_{0.1}$ response to carbon dioxide to 50% of control, a result similar to the reduction in ventilatory response (Jordan, 1981). Derènne and colleagues (1976) found that methoxyflurane anaesthesia reduced the ventilatory response to carbon dioxide but not the mouth occlusion pressure response, possibly implying that the main action of the anaesthetic was to impair the mechanical properties of the respiratory system rather than to depress the respiratory centres.

## TESTS OF CHEMOSENSITIVITY: RESPONSE TO HYPOXIA

Although acute changes in ventilation are predominantly under control of the feedback process involving regulation of carbon dioxide and hydrogen ion concentration, chronic adjustments of ventilation are often governed mainly by oxygen requirements. In patients with chronic carbon dioxide retention resulting from severe lung disease, the extracellular fluid pH in the brain and the blood pH may be near normal in spite of the increased arterial $P\text{CO}_2$. Most of the stimulus to breathing from the increased $P\text{CO}_2$ is therefore diminished and arterial hypoxaemia is the main drive to ventilation. Many drugs considerably depress the ventilatory response to hypercapnia and if they also depress the response to hypoxia then profound respiratory depression is likely.

Hypoxia stimulates ventilation primarily through its action on carotid body chemoreceptors and has no action on central chemoreceptors, other than a depressant effect in severe hypoxia. The ventilatory response to abrupt changes in oxygen tension is very rapid (approx. 10–20 s) and this provides a brisk protective reflex during events such as the upper airway obstruction that may occur during normal sleep (Bowes et al., 1981). A drug that depresses the response to hypoxia may therefore have deleterious effects on this protective reflex. In the overall assessment of the respiratory effects of pharmacological agents, testing the respiratory response to hypoxia would therefore seem highly relevant.

### *Steady-state methods*

The ventilatory response to hypoxia is measured by the subject breathing various fixed concentrations of oxygen for periods of at least 5–10 min before ventilation is measured. End-tidal $P\text{O}_2$, or preferably arterial $P\text{O}_2$, is used to quantitate the stimulus to breathing. It is usual to maintain end-tidal or arterial $P\text{CO}_2$ at a constant value during the increased ventilation produced by hypoxia by adjusting the inspired concentration of carbon dioxide. This method (Cormack, Cunningham and Gee, 1957) enables ventilation to be plotted as a function of $P\text{O}_2$ for each value of $P\text{CO}_2$. The resulting function can be reasonably fitted by a hyperbola, the shape of which reflects the sensitivity to hypoxia. Methods of processing such data are described in the next section. The results may also be plotted as shown in figure 2 as the ventilatory response to carbon dioxide at different but constant values of $P\text{O}_2$ (Cunningham et al., 1957; Lloyd, Jukes and Cunningham, 1958). The response to hypoxia may then be evaluated by comparing the slopes of the ventilatory response to carbon dioxide under conditions of differing $P\text{O}_2$. A further approach is to measure the difference in ventilation produced by arterial oxygen tensions of 6 kPa (40 mm Hg) and 25 kPa at resting arterial $P\text{CO}_2$, referred to as $\Delta \dot{V}_{40}$ (Sørensen and Severinghaus, 1968). This technique has the disadvantage that only one point during hypoxia is used, and this point is usually in a region where ventilation is likely to vary greatly with small changes in $P\text{O}_2$ or $P\text{CO}_2$ (Weil and Zwillich, 1976).

Equilibration of the arterial oxygen chemoreceptors with inspired oxygen is fairly rapid and the period of breathing required to reach a steady state may be reduced by first equilibrating with the inspired carbon dioxide. However, the steady-state tests involve rather prolonged exposure to hypoxia and may be hazardous to some patients. Methods have therefore been developed for assessing the ventilatory response to hypoxia which require somewhat shorter exposure to hypoxic gas mixtures.

### *Nonsteady-state methods*

The ventilatory response to isocapnic hypoxia may be derived as a continuous curve relating alveolar oxygen tension to minute volume by two basic methods.

*Progressive technique*

A gradual reduction of inspired oxygen concentration is achieved by the contolled addition of nitrogen to the inspired gas mixture and the addition of carbon dioxide to maintain $P\mathrm{CO}_2$ constant (Weil et al., 1970). The time taken for alveolar $P\mathrm{O}_2$ to reach 6–7 kPa is approximately 10–20 min and is controlled by the investigator.

*Rebreathing technique*

The subject rebreathes from a 6-litre bag containing an initial mixture of 30% oxygen, 7% carbon dioxide (approx. mixed venous concentration) and nitrogen (Rebuck and Campbell, 1974). Oxygen concentration in the circuit gradually decreases as a result of metabolic consumption while $P\mathrm{CO}_2$ is kept constant by manually adjusting the amount of rebreathed gas which passes through a carbon dioxide absorber. The time taken for alveolar $P\mathrm{O}_2$ to decrease to 6–7 kPa is approximately 4–6 min.

End-tidal oxygen may be measured using a rapidly responding fuel cell oxygen analyser (Weil, Sodal and Speck, 1967) or a mass spectrometer and the end-tidal carbon dioxide tension may be measured with a rapidly responding infra-red analyser or mass spectrometer. Ventilation may be measured using one of the methods described above. The rebreathing technique may utilize a "bag-in-bottle" to enable indirect measurement of ventilatory volumes and so avoid problems of the effects of changes in gas composition on the volume measuring device.

These methods yield data that are comparable to the steady-state technique, and have the advantage of being quicker to carry out. A hyperbolic relationship between ventilation and $P\mathrm{O}_2$ at constant $P\mathrm{CO}_2$ usually assumed and the equation for the hyperbola that best fits the data is calculated. This relationship can be described by the equation

$$\dot{V} = \dot{V}_0 + A/(P\mathrm{AO}_2 - C),$$

where $\dot{V}$ is minute ventilation, $\dot{V}_0$ is the value of ventilation if $P\mathrm{AO}_2$ (alveolar oxygen tension) were to approach infinity; $A$ is the parameter which determines the shape of the curve and $C$ is the value of $P\mathrm{AO}_2$ at which ventilation would approach infinity (fig. 5). The equation is applicable to data obtained by steady-state, progressive or rebreathing methods for assessing the isocapnic hypoxic ventilatory response. The effect of a change in chemoreceptor sensitivity to hypoxia is to alter the shape of the hyperbola and to change the value of $A$ (fig. 5).

The value of $C$ is usually taken as 4.27 kPa (32 mm Hg) and this enables $\dot{V}$ to be related to $1/(P\mathrm{AO}_2 - 4.27)$, resulting in a virtually linear relationship, with a slope $A$ and intercept $\dot{V}_0$ which may be determined by linear least-squares regression (Weil et al., 1970). It may, however, be preferable to use a curve-fitting method that does not assume a value for $C$ (Hey and Hey, 1960). When oxygen concentration is plotted against ventilation, a virtually linear relationship is seen (Weil et al., 1970) and the same applies to oxygen saturation as measured by ear oximetry (Rebuck and Campbell, 1974; Rebuck and Woodley, 1975) (fig. 6). This may therefore provide a suitable means of determining the hypoxic response when rapid oxygen analysis is unavailable or when end-tidal $P\mathrm{O}_2$ poorly reflects arterial $P\mathrm{O}_2$.

*Special precautions*

Many of the precautions stated above apply to testing the response to hypoxia. If the hypoxic response is to be measured at a $P\mathrm{CO}_2$ greater than the

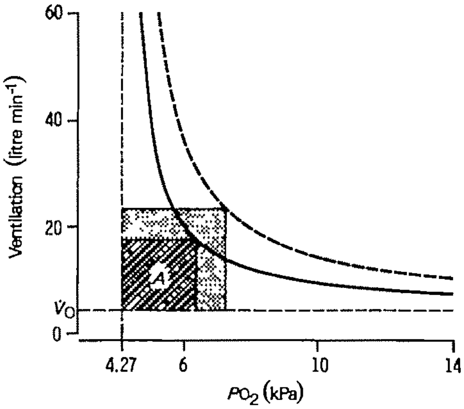

FIG. 5. Schematic diagram of the ventilatory response to hypoxia. The subject breathes progressively decreasing concentrations of oxygen at constant arterial carbon dioxide tension. Minute volume is plotted against oxygen tension and a hyperbola is fitted to the data (solid and broken curves). The broken curve represents a greater sensitivity to hypoxia as indicated by a greater value for parameter $A$ (stippled area *v.* hatched area). The curves have identical asymptotes $\dot{V}_0$ and $C$ (taken as 4.27 kPa).

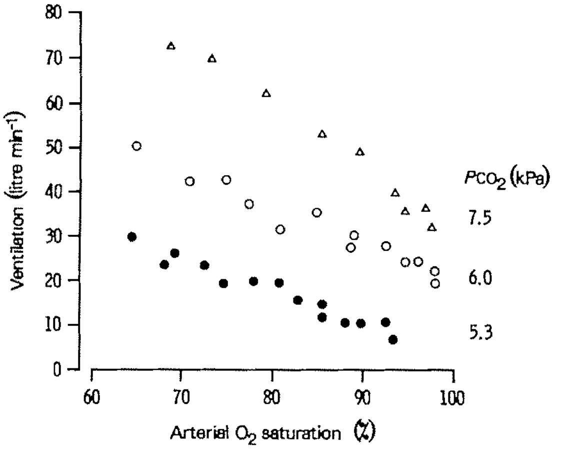

FIG. 6. Ventilatory response to hypoxia measured in one subject at three constant values of end-tidal carbon dioxide tension. Arterial oxygen saturation was measured non-invasively using an ear oximeter and shows an almost linear relationship with minute volume. Redrawn from Rebuck and Woodley (1975) by permission of the authors and the Editor of the *Journal of Applied Physiology*.

normal resting arterial value, a period of equilibration should be allowed (possibly 6–10 min) before inducing hypoxia (Read, Nickolls and Hensley, 1977). Because of the marked effect of a change in $P_{CO_2}$ on the hypoxic response, it is essential to control $P_{CO_2}$ within close limits during the test. As for the hypercapnic ventilatory response, the hypoxic ventilatory response is more variable between-days than within-days (Sahn et al., 1977) and therefore it is desirable to assess the effects of drugs over a short time course if possible, preferably using baseline data obtained on that day. It may well be that hypoxic ventilatory responses are log-normally distributed, as are hypercapnic ventilatory response, but this has not yet been proven.

Careful monitoring of the subject's cardiovascular status is required to prevent possible deleterious effects of hypoxia.

### *Tests of transient response to hypoxia*

Single or multiple breaths of nitrogen are administered and the resulting change in ventilation over the next 15–30 s is recorded. The test is rapid to perform, does not involve prolonged periods of hypoxia and therefore avoids the central depression sometimes produced. However, the response is small and lacks resolution and reproducibility unless the stimulus is combined with hypercapnia (15% carbon dioxide in nitrogen) (Kronenberg et al., 1972) or unless multiple response averaging techniques are used.

### *Examples of the effects of drugs on the response to hypoxia*

The few studies of the effects of drugs on the response to hypoxia in man have been mainly confined to testing the ventilatory response to progressive or rebreathing hypoxia. Weil and others (1975) showed that, in normal volunteers, morphine 7.5 mg produced a significant decrease in $A$ (to 40% of control), greater than the depression in the slope of the ventilatory response to carbon dioxide. A greater depression in the hypoxic response than the hypercapnic response following morphine 15 mg was also reported by Santiago and colleagues (1979). Hirshman and his colleagues (1975), also using progressive isocapnic hypoxia, showed that pentobarbitone has a depressant effect on $A$ in some individuals. Knill and Gelb (1978) showed that halothane virtually abolished the hypoxic response at 1.1 and 2 MAC concentrations, and caused a reduction to 28% of control at 0.1 MAC, suggesting that halothane has a more important effect on the hypoxic response than on the hypercapnic response. Similar observations were made for enflurane (Knill, Manninen and Clement, 1979).

Mouth occlusion pressure may be used to quantitate the change in ventilatory drive to breathing during hypoxia in a way similar to the method described for use during hypercapnia. Kryger and others (1976) found that pethidine depressed both the ventilatory and $P_{0.1}$ responses to hypoxia to a greater extent than the depression of the hypercapnic responses.

## MEASUREMENT OF RESPONSE TO ADDED MECHANICAL LOADS

Patients with obstructive airways disease, such as bronchial asthma, frequently exhibit greater than normal respiratory depression after narcotics (Crofton and Douglas, 1981) and it seems reasonable to establish whether loaded breathing *per se* has deleterious effects on ventilation which may be exacerbated by certain drugs (Pengelly, Rebuck and Campbell, 1973). Although loads may be added to breathing by inhalation of bronchoconstrictor agents, the ethics, logistics and interpretational problems considerably limit this method and it is more usual to apply some form of external mechanical load, of which there are three main types:

Resistive loads: where pressure across the load depends on flow rate through it. These resistances may be a simple narrow tube, but it is more usual to use a resistance that is roughly constant with flow over the normal range, such as a tube containing a series of fine wire mesh discs or uniformly packed cotton wool.

Elastic loads: where pressure across the load depends on the volume displacement. These are usually constructed from closed tanks or drums from which the subject breathes – the smaller the drum, the smaller the compliance.

Threshold loads: where pressure across the load is constant once a flow is established. These are most easily constructed from a pipe partially immersed in water at a depth set by the threshold pressure required.

The response to the load may be measured in terms of (a) its effect on volume, flow, pressure or timing, (b) changes in nervous activity at various sites or changes in pattern of movement of the chest wall, or both and (c) changes in blood-gases. The normal response depends on the type of load but generally it results in the maintenance of a nearly normal minute volume, even in the face of large loads. The normal response to an inspiratory resistive load is a prolongation of the inspiratory phase and a low inspiratory flow rate. The responses are conveniently divided into early and steady-state changes with chemical factors being important only in the latter. The early response to a mechanical load operates through the stretch receptors, muscle spindles and the intrinsic mechanical properties of the inspiratory pump (Cumming and Semple, 1980), whereas after one or two breaths the chemical drive to ventilation becomes increasingly important. A major factor governing the response to a load is the volitional or conscious response, especially as this may be modified by learning. Drugs may act at one or more points in the regulatory process or may interfere with the interaction of the various components. For example, an analgesic drug may interfere with chemosensitivity and thus alter the steady-state response to a load, but it may also interfere with the conscious interpretation of the load through its analgesic and sedative properties. Although the response to an extrinsic load in healthy subjects may be different to that in patients with intrinsic loads increased through pulmonary disease (Anthonisen, 1976), it may well be that drugs act in a similar way in both situations. Hence studying the change in responses to a load in normal subjects may give indications of the expected effects in patients with obstructive airways disease.

### *Examples of reported effects of drugs on loaded breathing*

The effects of drugs on loaded breathing are not always predictable from their effects on chemosensitivity. Normal subjects given the analgesic drug meptazinol showed no significant alteration in the ventilatory response to carbon dioxide, but end-tidal carbon dioxide tension during inspiratory resistive loading was increased to a similar value as during loading following an equivalent dose of morphine (Jordan et al., 1979). In contrast, diazepam was shown to depress the ventilatory response to carbon dioxide but did not adversely alter the response to an inspiratory resistive load (Jordan, Lehane and Jones, 1980).

Light general anaesthesia with methoxyflurane has been shown to reduce considerably the response to inspiratory resistive loading (Whitelaw et al., 1976) as indicated by relative lack of increases in drive and inspiratory time with loading. In a study on the effects of sub-anaesthetic concentrations of nitrous oxide on the response to inspiratory resistive loading in volunteers, a considerable reduction in the immediate (first breath) response to the load was found with nitrous oxide (Royston, Jordan and Jones, 1981). The normal prolongation of inspiratory time and increased tidal volume were not apparent with nitrous oxide (fig. 7) although inspiratory drive, as assessed by $V_T/T_I$, was unchanged. It is likely that the immediate response was largely consciously mediated and therefore that nitrous oxide reduced the awareness of the load. Indeed only two of the eight subjects in this study stated awareness of the load during 40% nitrous oxide. This relative lack of awareness to loading seems a recurring feature of analgesic drugs and may be important clinically as it may indicate possible failure of adequate response to partial or total upper airway obstruction. The effect was independent of altered chemosensitivity, since nitrous oxide does not depress the ventilatory response to carbon dioxide (Eckenhoff and Helrich, 1958; Yacoub et al., 1976).

A further important aspect of the load-compensating response is the stabilization of the chest wall against deformation or distortion in the face of loading, so that the respiratory muscles may function efficiently (Shannon and Zechman, 1972). For example, inspiratory loading can result in in-

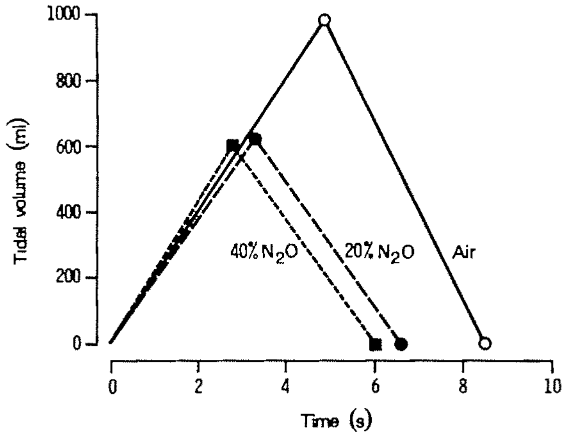

FIG. 7. The average respiratory cycle as in figure 1, showing the first loaded breath while subjects breathed air, 20% and 40% nitrous oxide. The mean data for eight subjects are shown and illustrate the lack of prolongation of inspiratory time with loading while breathing nitrous oxide and an unchanged inspiratory drive as indicated by an almost fixed slope of the inspiratory portion ($V_T/T_I$).

ward movement of the rib cage on inspiration as a result of large subatmospheric intrathoracic pressures produced predominantly by diaphragmatic contraction. Such paradoxical movement of the rib cage would require the diaphragm to contract more to produce a given tidal volume and may also alter the distribution of ventilation in the lung and lead to impaired ventilation–perfusion matching. Using the respiratory inductive plethysmograph in a study of the effects of nitrous oxide on loaded breathing, a marked increase in asynchronous breathing was found with 40% nitrous oxide (Royston, Jordan and Jones, 1982). Compared with air breathing measurements, there was a diminished rib cage contribution to tidal volume and an increased phase shift between rib cage and abdominal movement during loaded breathing on 40% nitrous oxide. It has also been shown that halothane anaesthesia depresses both phasic and tonic postural reflex activity of the rib cage, resulting in paradoxical movement during resistive loading (Jones et al., 1979).

The above reports are all concerned with the effect of a single stress applied to the ventilatory control system. It is possible to apply simultaneously multiple stresses to the system, for example loading and exercise (Demedts and Anthonisen, 1973) or loading and increased chemical drive (Kryger et al., 1976; Lopata et al., 1977). Santiago and others (1980) studied the respiratory response to hypercapnia with and without added inspiratory resistance and showed that acute administration of methadone abolished the augmentation of inspiratory drive (assessed by mouth occlusion pressure) normally seen with loaded breathing (fig. 8). In contrast, chronic methadone administration did not result in reduced response to the load and the authors therefore concluded that narcotic drugs may abolish the respiratory compensation although tolerance develops with chronic use. Meperidine has been shown to reduce the response to external resistance during hypercapnia and hypoxia, and this was interpreted as the drug producing "non-recognition" of the load or inhibiting the motor response to a load that was recognized (Kryger et al., 1976).

## ASSESSMENT OF RESPIRATORY EFFECTS OF DRUGS IN A CLINICAL ENVIRONMENT

With the possible exception of the anaesthetic agents, respiratory effects of drugs have been studied in detail only in normal subjects in the laboratory, with relatively few detailed reports of their effects on respiration in patients in the clinical environment. It is difficult to extrapolate with confidence from the effects of a drug on the regulation of breathing in normal subjects to the effect that it may have in patients in differing clinical situations. There are several practical problems in applying conventional

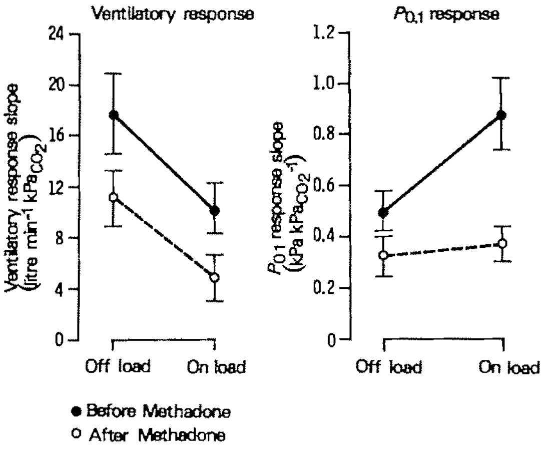

FIG. 8. Effects of methadone on the ventilatory and mouth occlusion responses to hypercapnia with and without inspiratory resistive loading. Methadone depressed the unloaded responses to hypercapnia and almost completely abolished the normal increase in the mouth occlusion pressure response to hypercapnia with loading. Redrawn from Santiago and others (1980) by permission of the authors and the Editor of the *American Review of Respiratory Disease.*

tests for assessing control of breathing in patients. In applying these tests it is usually necessary to familiarize the patient with the respiratory manoeuvres and apparatus beforehand and this is not always possible. The patients may be drowsy, confused or in pain and this will limit co-operation as well as influencing the results in an unpredictable fashion. A further important aspect is that it may be potentially hazardous to apply stress tests involving hypercapnia, hypoxia or mechanical loads in patients. During sleep the respiratory effects of drugs may further diminish normal reflex function (Forrest and Bellville, 1964; Sullivan et al., 1978), and so it is important to examine the effects of drugs on the control of breathing during sleep. Most conventional tests are applicable only to awake patients.

In the opinion of the author, it is more relevant to evaluate the action of clinically administered drugs on resting breathing in the undisturbed patient rather than on artificial challenges which would then require interpretation and extrapolation to situations that occur naturally. Measurements of normal resting breathing in the clinical environment play a vital role in the overall assessment of a pharmacological agent or particular method of administration and although many of the problems of applying conventional challenge tests in patients are avoided, new problems emerge which are challenging to the investigators.

### *Requirements of clinical assessment*

The effects of respiratory depressant drugs on the pattern of breathing are often quite marked, resulting for example in periodic breathing or in occasional apnoeic episodes. To detect these transient events it is necessary to make continuous measurements over periods of many hours. The monitoring methods should therefore be comfortable and unobtrusive to the patient, should require virtually no patient co-operation and should preferably be non-invasive.

*Measurement of ventilation.* Mouthpieces or tight-fitting face-masks enable direct measurement of ventilation, but they are poorly tolerated by patients for long periods of measurement, cause conscious awareness of breathing, increase deadspace and restrict movement. Mouthpieces have been shown to alter significantly the pattern of breathing (Gilbert et al., 1972). Methods which measure ventilation without direct connection to the airway are better suited to long-term continuous assessment of respiration. Techniques which measure changes in external dimensions of the torso may be calibrated against a direct method of volume measurement to yield quantitative data. Methods which enable the measurement of the separate contributions to breathing of the rib cage and abdomen–diaphragm are preferable as they also allow recognition of paradoxical or asynchronous breathing and separate identification of obstructive and central apnoeas. Most methods to date involve measurement of cross-sectional dimensions (e.g. anteroposterior and lateral dimensions using magnetometers) or circumference (e.g. using mercury-in-silastic strain gauge). As discussed earlier, there are limitations in the accuracy of such techniques in situations where the pattern of breathing or posture of the patient may change, or when distortion of the shape of the chest wall may occur (as in increased mechanical loading, such as airway obstruction). It may therefore be preferable to use the more recent approach of respiratory inductive plethysmography which is commercially available as Respitrace. The device is comfortable to wear and is ideally suited to long term recordings. It has been demonstrated to provide good accuracy of volume measurement over a wide range of body positions (Watson, 1980), and is frequently used in monitoring respiration during sleep both in adults in sleep disorder centres and in infants in special care units (Duffty et al., 1981).

In interpreting measurements of ventilation, it is often necessary to consider the state of consciousness of the patient. Unlike measurements of normal volunteers where periods of sleep should be avoided, measurements of resting breathing in patients in the normal clinical environment may encompass periods of differing sleep stage as well as wakefulness. It has been well documented that normal sleep significantly alters breathing, with different sleep states or stages having different effects (Bülow, 1963; Gothe et al., 1981). Care must be taken to ensure that changes in breathing induced by normal sleep should not be misinterpreted as drug effects. Further, it is possible that respiratory depressant drugs act synergistically with sleep to depress respiration seriously (Forrest and Bellville, 1964), and with depressed protective reflexes this could constitute a considerable hazard. In order to assess the interaction between sleep, drugs and respiration, recordings of the electroencephalogram (e.e.g.), electrooculogram (e.o.g.) and electromyogram (e.m.g.) may be analysed using conventional sleep staging techniques and criteria (Rechtschaffen and Kales, 1968; Agnew and Webb, 1972).

*Measurement of blood-gas tensions.* Direct methods of blood-gas measurement are invasive and unsuitable for continuous long-term measurements and it is preferable to use indirect methods. End-tidal $P\text{CO}_2$ may be sampled using a mass spectrometer or infrared carbon dioxide analyser, but if a mouthpiece or face-mask is to be avoided, the gas sampling line will need to be placed at the nares or in the nasopharynx with possible problems of air entrainment, moisture blockages and discomfort to the patient. Arterial oxygen saturation may be estimated using ear oximetry and this is a convenient and reasonably accurate method which is well suited to long term continuous measurements.

*Examples of respiratory effects of drugs in a clinical environment*

Gas exchange is often impaired in patients after anaesthesia and major surgery (Marshall and Wyche, 1972), so that the effects of respiratory depressant drugs may be more profound during the initial postoperative period. Consequently the assessment of respiration is necessary in the development and evaluation of improved techniques for providing analgesia after operation. There is currently much activity in this field, conventional opiate and the newly developed analgesics being administered as continuous i.v. infusions, as variable rate infusions in patient demand systems, and as intrathecal and extradural injections. Few studies have included a sufficiently comprehensive assessment of respiratory depression, most relying simply on intermittent measurements of respiratory rate and blood-gas tensions.

In a study of patients who had undergone cholecystectomy, respiratory inductive plethysmography was used to record respiration continuously for 24 h after surgery (Catling et al., 1980) and revealed that continuous i.v. infusion of papaveretum (mean dose 145 mg in 48 h) was associated with a greater frequency of apnoeic episodes and periods of low respiratory rates than conventional intermittent injections (81 mg in 48 h). Apnoeic periods lasting up to 40 s and rates as low as 6 b.p.m. were recorded.

In a subsequent study to investigate possible interactions between opiate analgesia, sleep and residual effects of anaesthesia, one group of patients received a continuous infusion of morphine following an i.v. pain relieving dose, and another group received intercostal nerve block vith bupivacaine (Catley et al., 1982). E.e.g., e.o.g., oxygen saturation using ear oximetry, and respiration using respiratory inductive plethysmography enabled disturbances in breathing to be quantitated and related to sleep state during the 16-h study period. Oxygen saturation frequently decreased to less than 80% in several patients receiving morphine, with most of these events being associated with periods of partial or total upper airway obstruction as indicated by paradoxical motion of rib cage or abdomen respiratory signals and by audible snoring in many cases (fig. 9). Many episodes of central apnoea were also observed although oxygen saturation never decreased to less than 89% during these events (fig. 10). The potentially most serious events were therefore associated with upper airway obstruction, presumably resulting from loss of tone of the muscles of the upper airway allowing the tongue to fall back or the pharyngeal walls to collapse (Guilleminault et al., 1978). These events always occurred during stages 1 or 2 of sleep and were usually terminated by an arousal or awakening (fig. 9). None of the patients were in stage 4 or REM sleep during the study and very few were in stage 3.

During periods of partial upper airway obstruction, tidal volume and minute volume were frequently seen to increase progressively during the episode whilst paradoxical chest wall movements increased and oxygen saturation decreased dramatically (fig. 11). This illustrates the inadequacy of simple measurements of rate or even tidal volume without provision for recognizing paradoxical breathing (i.e. separate rib cage and abdominal signals). The end-expiratory volume often decreased during such periods (fig. 11) and this may have contributed to the decrease in oxygen saturation. Continuous measurement of end-expiratory volume may therefore be informative in relating respiration to changes in oxygenation, particularly in patients with diminished lung volumes such as patients after abdominal surgery, or those with closing capacity near to or greater than functional residual capacity.

A further observation in this trial and in a similar study (Ford, et al., 1981) was that diaphragm function is often considerably depressed following upper abdominal surgery, even during adequate analgesia, so that patients become reliant on intercostal muscle activity. The preferential suppression by morphine of the rib cage contribution to breathing observed in normal volunteers by Rigg and Rondi (1981) and during sleep by Tusiewicz and colleagues (1977) could therefore be hazardous to such patients. In

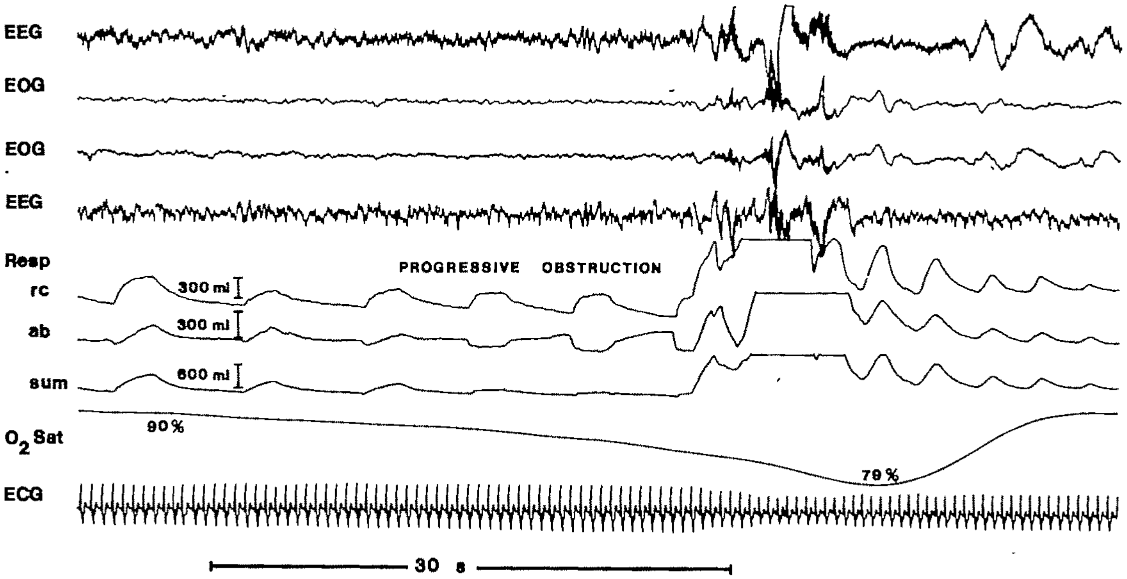

FIG. 9. Partial airway obstruction developing into obstructive apnoea in a patient receiving a morphine infusion for pain relief following total hip replacement. Note the paradoxical respiratory movements and the marked decrease in oxygen saturation terminated by an arousal (as indicated by the e.e.g. and e.o.g.) and the re-occurrence of normal breathing. The oxygen saturation trace is delayed by 10–15 s because of lung–ear circulation time and instrument response time.

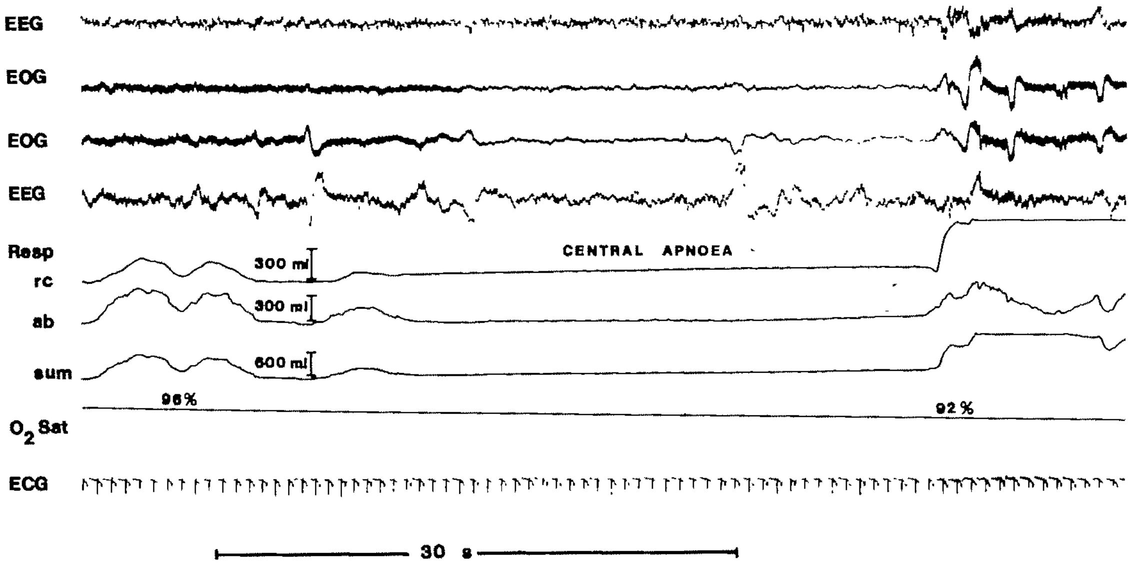

FIG. 10. Episode of central apnoea lasting 30 s in a patient who received an intercostal nerve block for pain relief after cholecystectomy. Note the relatively small decrease in oxygen saturation during the period of apnoea. The oxygen saturation trace is delayed by 10–15 s because of lung–ear circulation time and instrument response time.

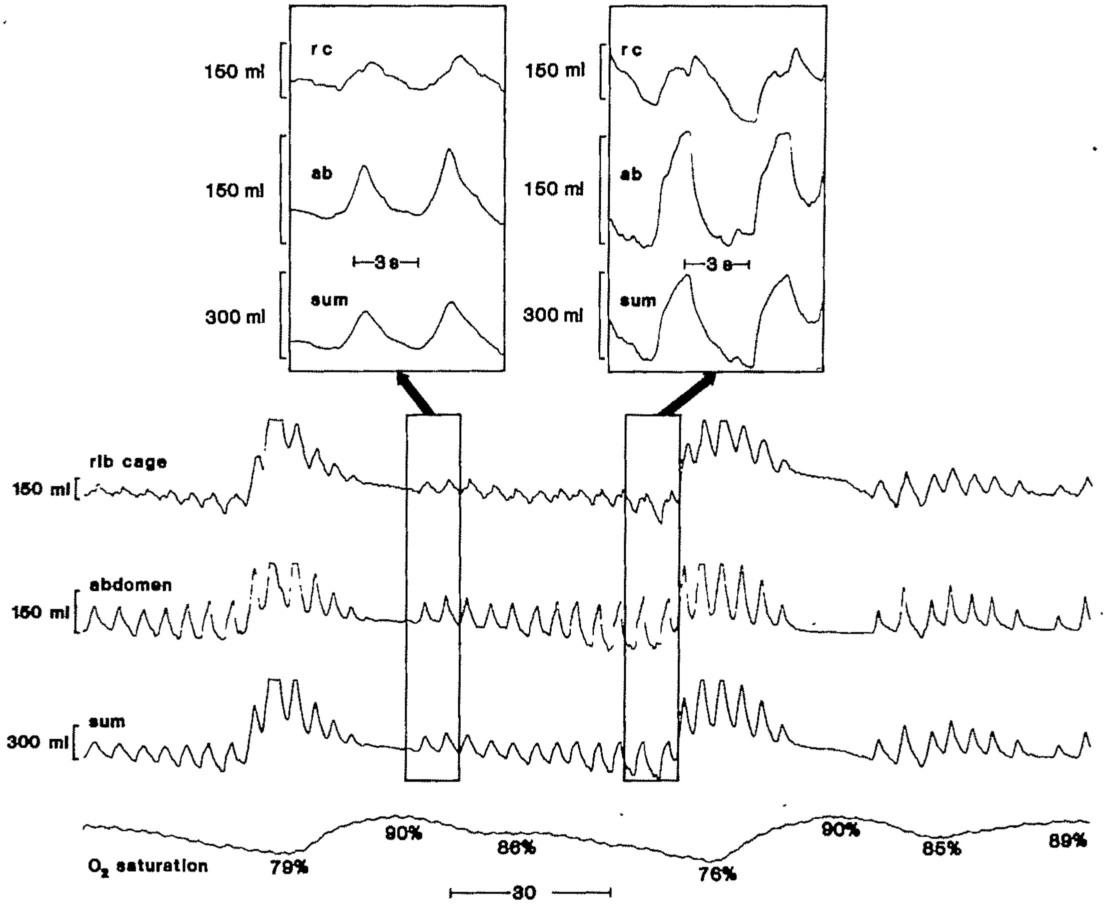

FIG. 11. Repeated episodes of paradoxical respiration (caused by partial upper airway obstruction) in a patient receiving morphine infusion for pain relief following total hip replacement. The marked decreases in oxygen saturation during periods of paradoxical respiration were terminated by hyperventilation and then followed by prolonged respiratory pauses (12 s and 17 s). Note the decreasing oxygen saturation despite the increasing ventilation during the periods of paradoxical respiration. The insets show two breaths at the beginning and end of a period of paradoxical respiration and indicate the development of paradoxical movement of the rib cage late in inspiration and early in expiration. The oxygen saturation trace is delayed by 10–15 s because of lung–ear circulation time and instrument response time.

addition, the suppression of chemosensitivity by morphine may account for the general impairment of blood-gas tensions found in patients receiving larger doses of papaveretum (Catling et al., 1980). It may also explain why patients receiving morphine analgesia appear to arouse from sleep at lower oxygen saturations during periods of apnoea and partially obstructed breathing than do patients receiving non-opiate analgesia (Catley et al., 1982).

## CONCLUSION

By utilizing techniques such as those used in the study of patients with disturbed breathing during sleep (e.g. sleep apnoea syndrome) the effects of drugs on both transient and steady-state respiration may be established in the clinical environment and such changes related to sleep state. Furthermore, it is evident that the results of tests in normal volunteers in the laboratory may be usefully applied to a particular clinical situation and that the two very different fields of assessment of respiratory effects of drugs can be complementary.

## REFERENCES

Agnew, H. W., and Webb, W. B. (1972). Sleep stage scoring. Abstract service of the American Psychological Association, Manuscript 293.

Altose, M. D., Kelsen, S. G., Stanley, N. N., Levinson, R. S., Cherniack, N. S., and Fishman, A. P. (1976). Effects of hypercapnia on mouth pressure during airway occlusion in conscious man. *J. Appl. Physiol.*, **40**, 338.

Anthonisen, N. R. (1976). Some steady-state effects of respiratory loads. *Chest*, **70**, (Suppl. 1), 168.

Ashutosh, K., Gilbert, R., Auchincloss, J. H., Erlebacher, J., and Peppi, D. (1974). Impedence pneumograph and magnetometer methods for monitoring tidal volume. *J. Appl. Physiol.*, **37**, 964.

Bowes, G., Townsend, E. R., Bromley, S. M., Kozar, L. F., and Phillipson, E. A. (1981). Role of the carotid body and of afferent vagal stimuli in the arousal response to airway occlusion in sleeping dogs. *Am. Rev. Respir. Dis.*, **123**, 644.

Bülow, K. (1963). Respiration and wakefulness in man. *Acta Physiol. Scand.*, **59**, (Suppl. 209), 1.

Catley, D. M., Thornton, C., Jordan, C., Royston, D., Lehane, J. R., and Jones, J. G. (1982). Postoperative respiratory depression associated with continuous morphine infusion. *Br. J. Anaesth.*, **54**, 235P.

Catling, J. A., Pinto, D. M., Jordan, C., and Jones, J. G. (1980). Respiratory effects of analgesia after cholecystectomy: comparison of continuous and intermittent papaveretum. *Br. Med. J.*, **281**, 478.

Cohn, M. A., Watson, H., Weisshault, R., Stott, F., and Sackner, M. A. (1978). A transducer for non-invasive monitoring of respiration; in *ISAM 1977, Proceedings of the Second International Symposium on Ambulatory Monitoring* (eds F. D. Stott, E. B. Raftery, P. Sleight and L. Goulding), p. 119. London: Academic Press Inc.

Cormack, R. S., Cunningham, D. J. C., and Gee, J. B. L. (1957). The effect of carbon dioxide on the respiratory response to want of oxygen in man. *Q. J. Exp. Physiol.*, **42**, 303.

Crofton, J., and Douglas, A. (1981). *Respiratory Diseases*, 3rd edn, p. 504. Oxford: Blackwell Scientific Publications.

Cumming, G., and Semple, S. J. (1980). *Disorders of the Respiratory System*, 2nd edn, p. 165. Oxford: Blackwell Scientific Publications.

Cunningham, D. J. C. (1974). Integrative aspects of the regulation of breathing: a personal view. MTP International Review of Science, Physiology Series 1, Vol. 2. *Respiratory Physiology* (ed. J. G. Widdicombe) p. 303. Butterworths: University Park Press.

—— Cormack, R. S., O'Riordan, J. L. H., Jukes, M. G. M., and Lloyd, B. B. (1957). An arrangement for studying the respiratory effects in man of various factors. *Q. J. Exp. Physiol.*, **42**, 294.

—— O'Riordan, J. L. H. (1957). The effect of a rise in the temperature of the body on the respiratory response to carbon dioxide at rest. *Q. J. Exp. Physiol.*, **42**, 329.

Demedts, M., and Anthonisen, N. R. (1973). Effects of increased external airway resistence during steady-state exercise. *J. Appl. Physiol.*, **35**, 361.

Dempsey, J. A. (1976). CO$_2$ Response: Stimulus definition and limitations. *Chest*, **70**, (Suppl. 1), 114.

Derenne, J. P., Couture, J., Iscoe, S., Whitelaw, W. A., and Milic-Emili, J. (1976). Occlusion pressures in men rebreathing CO$_2$ under methoxyflurane anesthesia. *J. Appl. Physiol.*, **40**, 805.

Douglas, N. J., Brash, H. M., Wraith, P. K., Calverley, P. M. A., Leggett, R. J. E., McElderry, L., and Flenley, D. C. (1979). Accuracy, sensitivity to carboxyhemoglobin, and speed of response of the Hewlett–Packard 47201A ear oximeter. *Am. Rev. Respir. Dis.*, **119**, 311.

Duffty, P., Spriet, L., Bryan, M. H., and Bryan, A. C. (1981). Respiratory induction plethysmography (Respitrace): An evaluation of its use in the infant. *Am. Rev. Respir. Dis.*, **123**, 542.

Eckenhoff, J. E., and Helrich, M. (1958). Effect of narcotics, thiopental and nitrous oxide upon respiration and respiratory response to carbon dioxide. *Anesthesiology*, **19**, 240.

Eldridge, F. L. (1975). Relationship between respiratory nerve and muscle activity and muscle force output. *J. Appl. Physiol.*, **39**, 567.

Engineer, S., and Jennett, S. (1972). Respiratory depression following single and repeated doses of pentazocaine and pethidine. *Br. J. Anaesth.*, **44**, 795.

Faithfull, D., Jones, J. G., and Jordan, C. (1979). Measurement of the relative contributions of rib cage and abdomen/diaphragm to tidal breathing in man. *Br. J. Anaesth.*, **51**, 391.

Ford, G. T., Whitelaw, W. A., Cruse, P. J., Rosenal, T., and Bosdech, L. (1981). Diaphragm function after upper abdominal surgery. *Am. Rev. Respir. Dis.*, **123**, (Suppl. 2), 186.

Forrest, W. H. jr, and Bellville, J. W. (1964). The effect of sleep plus morphine on the respiratory response to carbon dioxide. *Anesthesiology*, **25**, 137.

Gabel, R. A., Kronenberg, R. S., and Severinghaus, J. W. (1973). Vital capacity breaths of 5% or 15% CO$_2$ in N$_2$ or O$_2$ to test carotid chemosensitivity. *Respir. Physiol.*, **17**, 195.

Gilbert, R., Auchincloss, J. H., Brodsky, J., and Boden, W. (1972). Changes in tidal volume, frequency, and ventilation induced by their measurement. *J. Appl. Physiol.*, **33**, 252.

Gothe, B., Altose, M. D., Goldman, M. D., and Cherniack, N. S. (1981). Effect of quiet sleep on resting and CO$_2$-stimulated breathing in humans. *J. Appl. Physiol.*, **50**, 724.

Guilleminault, C., Hill, M. W., Simmons, F. B., and Dement, W. C. (1978). Obstructive sleep apnea: Electromyographic and fiberoptic studies. *Exp. Neurol.*, **62**, 48.

Hey, E. N., and Hey, M. H. (1960). The statistical estimation of a rectangular hyperbola. *Biometrics*, **16**, 606.

Hirshman, C. A., McCullough, R. E., Cohen, P. J., and Weil, J. V. (1975). Effect of pentobarbitone on hypoxic ventilatory drive in man. *Br. J. Anaesth.*, **47**, 963.

Hunter, A. R. (1967). Diazepam (Valium) as a muscle relaxant during general anaesthesia: a pilot study. *Br. J. Anaesth.*, **39**, 633.

Irsigler, G. B. (1976). Carbon dioxide response lines in young adults: the limits of the normal response. *Am. Rev. Respir. Dis.*, **114**, 529.

Jennett, S., Barker, J. G., and Forrest, J. B. (1968). A double-blind controlled study of the effects on respiration of pentazocine, phenoperidine and morphine in normal man. *Br. J. Anaesth.*, **40**, 864.

Johnson, L. F. jr, and Mead, J. (1963). Volume–pressure relationships during pressure breathing and voluntary relaxation. *J. Appl. Physiol.*, **18**, 505.

Jones, J. G., Faithfull, D., Jordan, C., and Minty, B. (1979). Rib cage movement during halothane anaesthesia in man. *Br. J. Anaesth.*, **51**, 399.

Jordan, C. (1981). Automatic method for measuring mouth occlusion pressure response to carbon dioxide inhalation. *Med.*

*Biol. Eng. Comput.*, **19**, 279.

Jordan, C., Jones, J. G., and Pinto, D. J. (1980). Postoperative respiration monitoring; in *ISAM 1979, Proceedings of the Third International Symposium on Ambulatory Monitoring*, p. 373. London: Academic Press.

—— Lehane, J. R., and Jones, J. G. (1980). Respiratory depression following diazepam: reversal with high-dose naloxone. *Anesthesiology*, **53**, 293.

—— —— Robson, P. J., and Jones, J. G. (1979). A comparison of the respiratory effects of meptazinol, pentazocine and morphine. *Br. J. Anaesth.*, **51**, 497.

Knill, R. L., and Gelb, A. W. (1978). Ventilatory responses to hypoxia and hypercapnia during halothane sedation and anesthesia in man. *Anesthesiology*, **49**, 244.

—— Manninen, P. H., and Clement, J. L. (1979). Ventilation and chemoreflexes during enflurane sedation and anaesthesia in man. *Can. Anaesth. Soc. J.*, **26**, 353.

Kronenberg, R., Hamilton, F. N., Gabel, R., Hickey, R., Read, D. J. C., and Severinghaus, J. (1972). Comparison of three methods for quantitating respiratory response to hypoxia in man. *Respir. Physiol.*, **16**, 109.

Kryger, M. H., Yacoub, O., and Anthonisen, N. R. (1975). Effect of inspiratory resistance on occlusion pressure in hypoxia and hypercapnia. *Respir. Physiol.*, **24**, 241.

—— —— Dosman, J., Macklem, P. T., and Anthonisen, N. R. (1976). Effect of meperidine on occlusion pressure responses to hypercapnia and hypoxia with and without external inspiratory resistence. *Am. Rev. Respir. Dis.*, **114**, 333.

Larson, C. P. jr, Eger, E. I., Muallem, M., Buechel, D. R., Munson, E. S., and Eisele, J. H. (1969). The effects of diethyl ether and methoxyflurane on ventilation: II a comparative study in man. *Anesthesiology*, **30**, 174.

Linton, R. A. F., Poole-Wilson, P. A., Davies, R. J., and Cameron, I. R. (1973). A comparison of the ventilatory response to carbon dioxide by steady-state and rebreathing methods during metabolic acidosis and alkalosis. *Clin. Sci. Molec. Med.*, **45**, 239.

Lloyd, B. B., Jukes, M. G. M., and Cunningham, D. J. C. (1958). The relation between alveolar oxygen pressure and the respiratory response to carbon dioxide in man. *Q. J. Exp. Physiol.*, **43**, 214.

Lopata, M., Evanich, M. J., and Lourenço, R. V. (1977). Relationship between mouth occlusion pressure and electrical activity of the diaphragm: Effects of flow-resistive loading. *Am. Rev. Respir. Dis.*, **116**, 449.

—— La Fata, J., Evanich, M. J., and Lourenço, R. V. (1977). Effects of flow-resistive loading on mouth occlusion pressure during $CO_2$ rebreathing. *Am. Rev. Respir. Dis.*, **115**, 73.

—— Zubillaga, G., Evanich, M. J., and Lourenço, R. V. (1978). Diaphragmatic EMG response to isocapnic hypoxia and hyperoxic hypercapnia in humans. *J. Lab. Clin. Med.*, **91**, 698.

Marshall, B. E., and Wyche, M. Q. (1972). Hypoxemia during and after anesthesia. *Anesthesiology*, **37**, 178.

Mead, J., Peterson, N., Grimby, G., and Mead, J. (1967). Pulmonary ventilation measured from body surface movements. *Science*, **156**, 1383.

Milic-Emili, J., and Aubier, M. (1980). Some recent advances in the study of the control of breathing in patients with chronic obstructive lung disease. *Anesth. Analg.* (Cleve.), **59**, 865.

—— Grunstein, M. M. (1976). Drive and timing components of ventilation. *Chest*, **70**, (Suppl. 1), 131.

Milledge, J. S., Minty, K. B., and Duncalf, D. (1974). On-line assessment of ventilatory response to carbon dioxide. *J. Appl. Physiol.*, **37**, 596.

Munson, E. S., Larson, C. P., Babad, A. A., Regan, M. J., Buechel, D. R., and Eger, E. I. (1966). The effects of halothane, fluroxene and cyclopropane on ventilation: A comparative study in man. *Anesthesiology*, **27**, 716.

Mustchin, C. P. (1977). Carbon dioxide rebreathing and mouth occlusion pressure measurements. *J. R. Coll. Physicians Lond.*, **12**, 87.

Ngai, S. H., Katz, R. L., and Farhie, S. E. (1965). Respiratory effects of trichlorethylene, halothane and methoxyflurane in the cat. *J. Pharmacol. Exp. Ther.*, **148**, 123.

Nunn, J. F. (1977). *Applied Respiratory Physiology*, 2nd edn. London: Butterworths.

Pengelly, L. D., Rebuck, A. S., and Campbell, E. J. M. (1973). Loaded breathing: in *Proceedings of an International Symposium on "The Effects of Mechanical Loads on Breathing"* (eds. E. J. M. Campbell, L. D. Pengelly and A. S. Rebuck). Edinburgh: Churchill Livingstone.

—— Tarshis, A. M., and Rebuck, A. S. (1979). Contribution of rib cage and abdomen–diaphragm to tidal volume during $CO_2$ rebreathing. *J. Appl. Physiol.*, **46**, 709.

Potter, D. R., and Payne, J. P. (1970). Newer analgesics: with special reference to pentazocine. *Br. J. Anaesth.*, **42**, 186.

Read, D. J. C. (1967). A clinical method for assessing the ventilatory response to carbon dioxide. *Australas. Ann. Med.*, **16**, 20.

—— Nickolls, P., and Hensley, M. (1977). Instability of the carbon dioxide stimulus under the "mixed venous isocapnic" conditions advocated for testing the ventilatory response to hypoxia. *Am. Rev. Respir. Dis.*, **116**, 336.

Rebuck, A. S. (1976). Measurement of ventilatory response to $CO_2$ by rebreathing. *Chest*, **70**, (Suppl. 1), 118.

—— Campbell, E. J. M. (1974). A clinical method for assessing the ventilatory response to hypoxia. *Am. Rev. Respir. Dis.*, **109**, 345.

—— Woodley, W. E. (1975). Ventilatory effects of hypoxia and their dependence on $P\text{CO}_2$. *J. Appl. Physiol.*, **38**, 16.

Rechtschaffen, A., and Kales, A. (eds) (1968). *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects.* Washington, D.C.: Public Health Service, U.S. Government Printing Office.

Remmers, J. E. (1976). Analysis of ventilatory response. *Chest*, **70**, (Suppl. 1), 134.

Rigg, J. R. A., and Rondi, P. (1981). Changes in rib cage and diaphragm contribution to ventilation after morphine. *Anesthesiology*, **55**, 507.

Royston, D., Jordan, C., and Jones, J. G. (1981). Effect of nitrous oxide on the adaptation to inspiratory resistive loading in man. *Br. J. Anaesth.*, **53**, 667P.

—— —— —— (1982). The effect of nitrous oxide and resistive loading on breathing patterns; in *ISAM 1981, Proceedings of the Third International Symposium on Ambulatory Monitoring* (eds F. D. Stott, E. B. Raftery, D. Clement, and S. L. Wright). London: Academic Press Inc.

Sackner, M. A. (ed.) (1980). *Diagnostic Techniques in Pulmonary Disease, Part I*, p. 503. New York: Marcel Dekker, Inc.

Sahn, S. A., Zwillich, C. W., Dick, N., McCullough, R. E., Lakshminarayan, S., and Weil, J. V. (1977). Variability of ventilatory responses to hypoxia and hypercapnia. *J. Appl. Physiol.*, **43**, 1019.

Santiago, T. V., Goldblatt, K., Winters, K., Pugliese, A. C., and Edelman, N. H. (1980). Respiratory consequencies of methadone: the response to added resistance to breathing. *Am. Rev. Respir. Dis.*, **122**, 623.

—— Johnson, J., Riley, D. J., and Edelman, N. H. (1979).

Effects of morphine on ventilatory response to exercise. *J. Appl. Physiol.*, **47**, 112.

Saunders, N. A., Powles, A. C. P., and Rebuck, A. S. (1976). Ear oximetry: Accuracy and practicability in the assessment of arterial oxygenation. *Am. Rev. Respir. Dis.*, **113**, 745.

Severinghaus, J. W. (1976). Proposed standard determination of ventilatory response to hypoxia and hypercapnia in man. *Chest*, **70**, (Suppl. 1), 129.

Shaffer, T. H., Altose, M. D., Lederer, D. H., and Cherniack, N. S. (1977). The interaction of FRC and ventilation on occlusion pressure in conscious man. *IEEE Trans. Biomed. Eng.*, **24**, 444.

Shannon, R., and Zechman, F. W. (1972). The reflex and mechanical response of the inspiratory muscles to an increased airflow resistance. *Respir. Physiol.*, **16**, 51.

Sohrab, S., and Yamashiro, S. M. (1980). Pseudorandom testing of ventilatory response to inspired carbon dioxide in man. *J. Appl. Physiol.*, **49**, 1000.

Sørensen, S. C., and Severinghaus, J. W. (1968). Respiratory sensitivity to acute hypoxia in man born at sea level living at high altitude. *J. Appl. Physiol.*, **25**, 211.

Sorkin, B., Rapoport, D. M., Falk, D. B., and Goldring, R. M. (1980). Canopy ventilation monitor for quantitative measurement of ventilation during sleep. *J. Appl. Physiol.*, **48**, 724.

Sullivan, C. E., Murphy, E., Kozar, L. F., and Phillipson, E. A. (1978). Waking and ventilatory responses to laryngeal stimulation in sleeping dogs. *J. Appl. Physiol.*, **45**, 681.

Tusiewicz, K., Bryan, A. C., and Froese, A. B. (1977). Contributions of changing rib cage–diaphragm interactions to the ventilatory depression of halothane anesthesia. *Anesthesiology*, **47**, 327.

—— Moldofsky, H., Bryan, A. C., and Bryan, M. H. (1977). Mechanics of the rib cage and diaphragm during sleep. *J. Appl. Physiol.*, **43**, 600.

Ward, S. A., and Cunningham, D. J. C. (1977). Separation of the inspiratory and expiratory reflex effects of alternate-breath oscillation of $P\mathrm{A}_{\mathrm{CO}_2}$ during hypoxia. *Respir. Physiol.*, **29**, 379.

Watson, H., (1980). The technology of respiratory inductive plethysmography; in *ISAM 1979, Proceedings of the Third International Symposium on Ambulatory Monitoring* (eds F. D. Stott, E. B. Raftery and L. Goulding), p. 537. London: Academic Press Inc.

Weil, J. V., Byrne-Quinn, E., Sodal, I. E., Friesen, W. O., Underhill, B., Filley, C. F., and Grover, R. F. (1970). Hypoxic ventilatory drive in normal man. *J. Clin. Invest.*, **49**, 1061.

—— McCullough, R. E., Kline, J. S., and Sodal, I. E. (1975). Diminished ventilatory response to hypoxia and hypercapnia after morphine in normal man. *N. Engl. J. Med.*, **292**, 1103.

—— Sodal, I. E., and Speck, R. P. (1967). A modified fuel cell for the analysis of oxygen concentration of gases. *J. Appl. Physiol.*, **23**, 419.

—— Zwillich, C. W. (1976). Assessment of ventilatory response to hypoxia. *Chest*, **70**, (Suppl. 1), 124.

Whitelaw, W. A., Derenne, J. P., Couture, J., and Milic-Emili, J. (1976). Adaptation of anesthetized men to breathing through an inspiratory resistor. *J. Appl. Physiol.*, **41**, 285.

—— —— Milic-Emili, J. (1975). Occlusion pressure as a measure of respiratory center output in conscious man. *Respir. Physiol.*, **23**, 181.

Wright, B. M., and Callan, K. (1980). A new respiratory recording and monitoring system; in *ISAM 1979, Proceedings of the Third International Symposium on Ambulatory Monitoring* (eds F. D. Stott, E. B. Raftery and L. Goulding), p. 329. London: Academic Press Inc.

Yacoub, O., Doell, D., Kryger, M. H., and Anthonisen, N. R. (1976). Depression of hypoxic ventilatory response by nitrous oxide. *Anesthesiology*, **45**, 385.

Yoshida, A., Hayashi, F., Sasaki, K., Masuda, Y., and Honda, Y. (1981). Analysis of pressure profile in the occluded airway obtained at the beginning of inspiration in steady state hypercapnia. *Am. Rev. Respir. Dis.*, **124**, 252.

Zubillaga, G., Lopata, M., Evanich, M. J., and Lourenço, R. V. (1976). Diaphragmatic EMG ($\mathrm{EMG}_{\mathrm{di}}$) response to isocapnic hypoxia in normal man: comparison to hyperoxic hypercapnia. *Am. Rev. Respir. Dis.*, **113**, 216P.

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# PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

## OXFORD MEETING

### CARDIORESPIRATORY EFFECTS OF AN INSPIRATORY HOLD AND CONTINUOUS POSITIVE PRESSURE VENTILATION IN GOATS

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Continuous positive pressure ventilation (CPPV) is used frequently to increase arterial $P\text{O}_2$ in patients with severe lung diseases. The use of CPPV is associated with a reduction in cardiac output, high peak airway pressures and a redistribution of blood flow from well to poorly ventilated parts of the lung. An alternative technique is to increase the inspiratory:expiratory time ratio (I:E) by adding an inspiratory hold (IPPVH). It is not clear whether the improvement in oxygenation with the latter technique results from opening of unstable alveoli during the prolonged inspiration or from an increase in functional residual capacity (FRC) secondary to incomplete emptying of the lung. The present experiments were designed to compare the cardiorespiratory effects of IPPVH (with no increase in FRC) with CPPV. To minimize differences resulting from changes in cardiac output the mean airway pressure during CPPV was adjusted to produce the same mean airway pressure as during IPPVH.

Sixteen goats (mean body weight 17.8 kg) were anaesthetized with thiopentone 30 mg kg$^{-1}$ i.v. The trachea was intubated and the lungs ventilated with 1.5% halothane in air (eight animals). In a further eight goats (submitted to lung damage induced by oleic acid) oxygen was substituted for the air. Tracheotomy was performed and catheters were placed to measure mean aortic ($P\overline{\text{AO}}$), pulmonary artery ($P\overline{\text{PA}}$) and wedge pressures ($P\overline{\text{W}}$), right atrial pressure ($P\text{RA}$), airway ($P\text{AW}$) and oesophageal pressure ($P\text{oes}$) and cardiac output ($\dot{Q}\text{t}$). Pulmonary and aortic blood samples were analysed for pH, $P\text{O}_2$, $P\text{CO}_2$ and Hb. Aortic and pulmonary artery oxygen contents were determined on a Lex-$\text{O}_2$-Con and the mean of two readings used to determine $\dot{Q}\text{s}/\dot{Q}\text{t}$. Ventilation was controlled with a tidal volume ($V\text{T}$) of 22 ml kg$^{-1}$ at a rate of 8–10 b.p.m. The ventilator generated a constant inspiratory flow pattern by means of a cam, rocker arm and bellows; the I:E ratio being controlled by two solenoid valves activated by microswitches. The ventilatory pattern was then changed from IPPV to IPPVH or CPPV in random order.

In the eight animals with normal lungs IPPVH reduced $V\text{D}/V\text{T}$ and $P\text{a}_{\text{CO}_2}$, but there were no changes in oxygenation. In a further eight animals with lung damage, both IPPVH and CPPV produced similar changes in $V\text{D}/V\text{T}$ and $P\text{a}_{\text{CO}_2}$. However, $P\text{a}_{\text{O}_2}$ during CPPV was significantly greater than during IPPVH or IPPV; $\dot{Q}\text{s}/\dot{Q}\text{t}$ was reduced significantly by both CPPV and IPPVH, but the effect was most marked with CPPV.

In the present experiments, frequency, tidal volume and inspiratory flow were unchanged during the different modes of ventilation. Since FRC was similar during IPPV and IPPVH, but increased by 500 ml during CPPV, it appears that the increase in lung volume resulting from the increase in FRC is more important than the duration of inspiration in improving oxygenation in this animal model.

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### A MICROCOMPUTER BASED TECHNIQUE FOR THE MEASUREMENT OF RESPIRATORY DEPRESSION IN POSTOPERATIVE PATIENTS

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The possibility of delayed respiratory depression is the major hindrance to the more widespread use of extradural morphine in the management of postoperative pain.

Early studies demonstrated either no obvious depression of ventilation or no significant increases in arterial $P\text{CO}_2$ and, therefore, could not define the basis for the rare occurrence of profound respiratory depression. However, a more recent study, in volunteers not undergoing surgery, did show differences in the degree and time-course of respiratory depression between i.v. and extradural morphine as assessed by the ventilatory response to rebreathing carbon dioxide (Nielsen et al., 1981). However, there is good reason to believe that ventilation may not be the most appropriate measure of respiratory drive in patients following abdominal surgery, since the alterations in pulmonary mechanics and the limitations of imperfect analgesia may depress ventilation independently of alterations in respiratory drive.

Two measures of respiratory drive which are less dependent on alterations in pulmonary mechanics have been described: (a) The occlusion pressure at 100 ms ($P_{0.1}$) (Whitelaw, Derenne and Milic-Emili, 1975); (b) The maximum rate of increase of isometric inspiratory pressure (Matthews and Howell, 1975). The former is used more widely, but demands intermittent occlusions of the patient's inspiratory airway. The latter is less well validated, but allows breath-by-breath measurement. The merits of these two techniques may be combined by measuring $P_{0.1}$ breath by breath utilizing transient occlusion of the airway. The method

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to be described is based on a rebreathing technique with the following modifications. A solenoid shutter which can be closed by a signal from a modified pneumotachograph (VP5, Mercury Electronics) is placed at the proximal end of the inspiratory limb. Ventilation is measured by a non-heated flow head placed in the outlet from the glass bottle which encloses the rebreathing bag. Analog voltages are relayed from the VP5 and a capnograph to a microcomputer via an analog-to-digital converter. Closure and opening of the solenoid shutter is controlled by the microcomputer via the VP5. The start of inspiration is detected by an increase in negative pressure (>0.02 kPa) measured proximal to the shutter. The pressure at 100 ms is recorded and the valve opened at 120 ms. Tidal volume is measured during inspiration and end-tidal carbon dioxide concentration during expiration.

The technique permits breath-by-breath measurements of $P_{0.1}$, instantaneous minute ventilation and end-tidal carbon dioxide concentration. Some preliminary data from patients given extradural morphine following surgery will be presented.

REFERENCES

Matthews, A. W., and Howell, J. B. L. (1975). *Clin. Sci. Molec. Med.*, **91**, 57.

Nielsen, C. H., Camporesi, E. M., Bromage, P. R., Bukowski, E. M., and Durant, P. A. C. (1981). *Anesthesiology*, **55**, A372.

Whitelaw, W. A., Derenne, J. P., and Milic-Emili, J. (1975). *Respir. Physiol.*, **23**, 181.

## RESIDUAL VOLUME CHANGE FOLLOWING OXYGEN BREATHING

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Nunn and his colleagues showed, in 1978, that breathing 100% oxygen for 10 min at normal lung volume followed by 5 min at a reduced lung volume led, in most subjects, to a reduction in functional residual capacity (FRC), a reduction in arterial oxygen tension and radiological evidence of basal collapse. As part of a study on the effects of oxygen/nitrogen ratios on postoperative hypoxia we have examined, in normal volunteers, changes in FRC, residual volume (RV) and closing capacity (CC) to check our methodology before studying patients.

Nineteen healthy non-trained volunteers were studied. Standard full lung volume measurements were performed using wedge spirometry, helium dilution and nitrogen excretion methods both before and after 15 min breathing 100% oxygen in a sitting position. During the first 10 min of this period, the chest was held at normal lung volumes; during the subsequent 5 min the subject breathed at a lung volume reduced by an amount approximately equal to normal tidal volume, as gauged by a signal from a mercury strain gauge placed around the lower thorax and displayed so that the subjects could monitor their own restricted breathing.

FRC and RV were decreased significantly following this breathing technique (table I) although there was no significant difference in expiratory reserve volume (ERV). There was no significant difference in the pre-oxygen FRC−CC volumes for those subjects whose FRC decreased in comparison with those in whom FRC remained the same or increased.

No previous study has shown that the residual volume following oxygen breathing has decreased, although previous studies (Nunn et al., 1965; Burger and Macklem, 1968; Nunn et al., 1978) have suggested that this was occurring. The present study with minimal restriction to breathing again emphasizes the dangers of restricted ventilation and high oxygen concentrations.

Table I.

| | Before $O_2$ breathing | After $O_2$ breathing | | | |
|---|---|---|---|---|---|
| | Mean ± SD (litre) | Mean ± SD (litre) | d.f. | Paired *t* test | *P* |
| FRC | 3.18 ± 0.69 | 3.07 ± 0.72 | 18 | 2.91 | <0.01 |
| RV | 1.50 ± 0.38 | 1.43 ± 0.38 | 18 | 2.63 | <0.02 |
| ERV | 1.68 ± 0.48 | 1.64 ± 0.54 | 18 | 0.98 | n.s. |

REFERENCES

Burger, E. J., and Macklem, P. (1968). *J. Appl. Physiol.*, **25**, 139.

Nunn, J. F., Coleman, A. J., Sachithanandan, T., Bergman, N. A., and Laws, J. W. (1965). *Br. J. Anaesth.*, **37**, 3.

——Williams, I. P., Jones, J. G., Hewlett, A. M., Hulands, G. H., and Minty, B. D. (1978). *Br. J. Anaesth.*, **50**, 91.

## EFFECTS OF DOPAMINE AND DOBUTAMINE ON THE DISTRIBUTION OF PULMONARY BLOOD FLOW DURING LOBAR VENTILATION HYPOXIA AND LOBAR COLLAPSE

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Regional alveolar hypoxia produced by ventilating a lobe of a lung with a hypoxic gas mixture or collapsing the lobe, causes pulmonary hypoxic vasoconstriction. This reduces blood flow through the hypoxic area and minimizes the decrease in $P_{O_2}$. It has been shown (Marin et al., 1979; Orchard, 1980) that inotropic drugs, including dopamine and dobutamine, reverse the response to alveolar hypoxia and increase blood flow to the hypoxic area, hence reducing arterial $P_{O_2}$ still further. This study compares the effects of dopamine and dobutamine when the left lower lobe of the dog is ventilated with a hypoxic mixture at normal values of $P_{CO_2}$ and when the lobe is atelectatic and $P_{CO_2}$ is increased.

Fifteen dogs were anaesthetized with thiopentone and pentobarbitone and the lungs ventilated mechanically with 100% oxygen. A left thoracotomy was performed and electromagnetic flow probes placed around the pulmonary artery trunk and left lower lobe artery. The lobar bronchus was intubated so that it could be ventilated independently with 100% oxygen or 7% oxygen. Catheters were inserted for measurement of aortic, pulmonary arterial and left atrial pressures. In eight dogs, dopamine $5\,\mu g\,kg^{-1}\,min^{-1}$ and $20\,\mu g\,kg^{-1}\,min^{-1}$, and in seven dogs dobutamine $5\,\mu g\,kg^{-1}\,min^{-1}$ and $20\,\mu g\,kg^{-1}\,min^{-1}$ were administered during lobar ventilation hypoxia with 7% oxygen in nitrogen and during collapse produced by occlusion of the left lower lobe bronchial tube after ventilation with 100% oxygen for 30 min. The flow to the lobe was expressed as a fraction of total blood flow ($\dot{Q}l/\dot{Q}t$).

$\dot{Q}l/\dot{Q}t$ decreased during ventilation hypoxia and was reduced further during collapse. When dopamine and dobutamine 20 $\mu g\,kg^{-1}\,min^{-1}$ were administered, $\dot{Q}l/\dot{Q}t$ increased significantly during both ventilation hypoxia and collapse. Cardiac output and $P\bar{v}O_2$ increased and $PaO_2$ decreased further with the infusion of both drugs. Pulmonary artery pressure was significantly increased during the high-dose dopamine infusion. Left atrial pressure did not change throughout the experiment. The increase in aortic pressure was significantly greater with dopamine than with dobutamine.

We conclude that dopamine and dobutamine increase the proportion of blood flow distributed to the lobe during ventilation hypoxia and collapse. The mechanism by which these drugs achieve their effect is still open to conjecture.

REFERENCES

Marin, J. L. B., Orchard, C., Chakrabarti, M. K., and Sykes, M. K. (1979). *Br. J. Anaesth.*, 51, 303.

Orchard, C. H. (1980). University of London PhD. Thesis.

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## MEASUREMENT OF OXYGEN UPTAKE: A NEW SYSTEM FOR THE MEASUREMENT OF OXYGEN UPTAKE DURING NITROUS OXIDE IN OXYGEN ANAESTHESIA

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The use of nitrous oxide during conventional general anaesthesia makes measurement of oxygen uptake ($\dot{V}O_2$) difficult. Closed circuit anaesthesia allows $\dot{V}O_2$ to be monitored under these circumstances.

A constant volume closed circuit in which gas concentrations were maintained by manual adjustment of nitrous oxide input has been described (Engstrom, Herzog and Norlander, 1961). We have developed a completely closed anaesthetic system (Beatty et al., 1982) modified for the present study to allow oxygen input via a precision metering valve and nitrous oxide input via a demand valve. The circuit maintains a constant volume for each stage of the ventilatory cycle, by allowing gas entry from the demand valve in response to a reduction in the resting circuit volume. Expired carbon dioxide is absorbed by soda-lime and nitrogen can be removed intermittently by flushing. Circuit gas concentrations are monitored using a mass spectrometer (VG Micromass Q701B) and displayed using a Grass polygraph. The sources of gas loss (which include sampling by the mass spectrometer) are quantified at the beginning of the monitoring session by adjusting the oxygen input, to eliminate demand while ventilating a test lung.

Oxygen input is initially set at a value estimated for the patient (Nunn, 1977) and adjusted if necessary. The total volume of the circuit and the patient FRC are measured using a nitrogen dilution technique. In the presence of a constant oxygen concentration, $\dot{V}O_2$ values can be obtained directly from the oxygen input after correcting for circuit losses. Alternatively the rate of change of oxygen concentration allows $\dot{V}O_2$ to be calculated. Detailed analysis of the oxygen traces is performed using an Apple Graphics Tablet with accompanying software, enabling digitization and analysis of the data and yielding estimations each 30 s, which are then plotted against time. The continuous record allows identification and quantification of transient changes in $\dot{V}O_2$. The method has been confirmed in the laboratory using a model lung with known extraction rates for nitrous oxide and oxygen. A rapid response to changes in simulated $\dot{V}O_2$ has been confirmed. The presence of another absorbable gas does not affect accuracy.

This new system of continuously monitoring $\dot{V}O_2$ is simple to use and accurate, and is non-invasive in the anaesthetized patient. The method has been used to study the effects of agents used routinely during general anaesthesia on $\dot{V}O_2$.

REFERENCES

Beatty, P., Wheeler, M. F. S., Kay, B., Greer, W., Cohen, A. T., and Parkhouse, J. (1982). *Br. J. Anaesth.*, 54, 689.

Engstrom, C. G., Herzog, P., and Norlander, O. (1961). *Acta Anaesthesiol. Scand.*, 5, 115.

Nunn, J. F. (1977). *Applied Respiratory Physiology*, p. 181. Butterworth & Co.

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## AN EVALUATION OF THREE FIXED PERFORMANCE OXYGEN MASKS – A NEW APPROACH

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Leigh (1970) introduced the concept that oxygen masks may be classified as fixed or variable performance devices. The method described by Leigh involved the measurement of the concentrations of oxygen and carbon dioxide in multiple samples of expired gas, while volunteers breathed the mixture delivered by various oxygen masks. A different method of investigation was undertaken by Cox and Gilbe (1981). They simulated respiration by using a Cape ventilator attached to a dummy face. A difference in performance was found between two types of mask, the Ventimask and the Bard Inspiron Accurox, both of which utilize the Venturi principle. This was attributed to the difference in volume of the two masks.

In this study an approach has been adopted similar to that described by Leigh. Four volunteers breathed the gas mixture delivered by the various concentrations of Ventimask Mark 2, Ventimask Mark 3, and the Bard Inspiron Accurox masks. Inspired and expired gas was sampled continuously and the concentration of oxygen and carbon dioxide measured by a Centronic MGA200 Mass Spectrometer and recorded on FM tape. The inspiratory flow rate was measured by the use of the inductance pneumograph described by Hill, Blackburn and Williams (1982), and the signal recorded on a Hewlett–Packard eight-channel recorder. The concentration of oxygen and carbon dioxide was subsequently replayed on an *X–Y* recorder and a gas R-line was obtained. This was correlated with peak inspiratory flow rate for each breath.

When the peak inspiratory flow rate was less than the total gas flow delivered from the mask under study, the gas R-line was a single line and the inspired oxygen concentration was obtained at zero carbon dioxide. When the peak inspiratory flow rate exceeded the total gas flow rate from the mask, the R-line opened out to a loop. Under these circumstances the inspired oxygen concentration decreased. Inspired oxygen concentration decreased to a greater extent as the oxygen concentration delivered by the mask increased.

Our results differ from those of Leigh (1970) in that the concentration of oxygen delivered by the Ventimasks Mark 2, Mark 3 or Bard Inspiron Accurox mask, were not within ± 2% of the nominal oxygen concentration. However, all three devices are fixed performance for the concentration delivered unless the peak inspiratory flow rate exceeds the total gas flow delivered by the mask. Our findings do not agree with those of Cox and Gilbe (1981), who found that the Bard Inspiron Accurox was not a fixed performance mask. On the contrary, the Bard Inspiron Accurox mask performed best in our study because of the higher oxygen priming flows recommended for use with these masks.

REFERENCES

Cox, D., and Gilbe, C. (1981). *Anaesthesia*, 36, 958.
Hill, S. L., Blackburn, J. P., and Williams, T. (1982). *Med. Biol. Eng. Comp.* (in press).
Leigh, J. M. (1970). *Anaesthesia*, 25, 210.

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## INFLUENCE OF AGE AND WEIGHT ON THE PRESSURE REVERSAL OF METHOHEXITONE IN THE RAT

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The variation in anaesthetic potency of the inhalation agents with age has been well documented in man (Stevens et al., 1975). We wish to report the effect of varying either age or weight on the anaesthetic potency of methohexitone at both ambient and increased pressures. Four groups of five male Sprague–Dawley rats were raised with *ad lib* or restricted (80% of *ad lib* intake) diets, and experiments carried out at either 12 or 24 weeks age. Methohexitone was infused continuously via a cannulated tail vein; rectal temperature was maintained at 37 ± 0.5 °C. Heart rate and respiration were recorded and anaesthesia ($AD_{95}$) was assessed every 5 min by noting the response to electrical stimulation. Once a stable level of anaesthesia was established and maintained for at least 20 min, pressurization was started (1 ATA $min^{-1}$) using helium. Inspired $P_{O_2}$ was 0.5 ATA, $P_{CO_2} < 0.001$ ATA.

TABLE II. *Rat weights and methohexitone anaesthetizing doses at ambient and increased pressures*

| | *Ad lib* diet (SEM) | Restricted diet (SEM) | *P* |
|---|---|---|---|
| 12 weeks age | | | |
| Rat weight (g) | 487 (17) | 378 (10) | <0.001 |
| Dose at 1 ATA ($mg\ kg^{-1}\ min^{-1}$) | 0.638 (0.009) | 0.832 (0.035) | <0.001 |
| Percentage of control $AD_{95}$ (at 40 ATA) | 164.3 (5.7) | 138.7 (13.3) | 0.1 |
| 24 weeks age | | | |
| Rat weight (g) | 657 (15) | 459 (16) | <0.001 |
| Dose at 1 ATA ($mg\ kg^{-1}\ min^{-1}$) | 0.606 (0.028) | 0.561 (0.018) | n.s. |
| Percentage of control $AD_{95}$ (at 40 ATA) | 148.9 (4.6) | 152.3 (5.8) | n.s. |

The data on anaesthetic potency are shown in table II. Over this pressure range the decrease in potency was found to be linear. In spite of the correction for weight of the rat in all the data, there was a significant increase in control doses between the restricted and *ad lib* diet groups at 12 weeks. However, the degree of pressure reversal was significantly decreased in the restricted diet group. In contrast there were no significant differences between the groups aged 24 weeks at either ambient or increased pressure.

In these experiments we have attempted to distinguish between the effects of age and weight. The data are consistent with the hypothesis that the nature of the molecular site of action of methohexitone in young adult animals is different to that of elderly animals.

REFERENCE

Stevens, W. C., Dolan, W. M., Gibbons, R. T., White, A., Eger, E. I. II, Miller, R. D., de Jong, R. H., and Elashoff, R. M. (1975). *Anesthesiology*, 42, 197.

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## LACTATE AND HAEMODYNAMIC CHANGES IN EARLY SHOCK

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The identification of factors providing an accurate prediction of outcome in severe shock would aid the evaluation of new therapeutic methods and might lead to more efficient use of scarce resources. The level of arterial blood lactate has been suggested as one accurate predictor of prognosis (Ruiz, Weil and Carlson, 1979).

In this prospective clinical study we have assessed the value of measurement of whole blood lactate in determining outcome during the acute phase of shock. The measurements were obtained in 30 patients suffering from shock of varying aetiology (20 septic, five cardiogenic, three haemorrhagic, two mixed). Arterial whole blood lactate, mean arterial pressure, urine volume, and core–peripheral temperature difference were measured on admission to the I.C.U. and at 3 and 24 h later.

Fifteen of the 30 patients in the study survived. There were no significant differences between survivors and non-survivors in either lactate or haemodynamic values at the time of admission. In the survivors (table III) after 3 h of resuscitation there were statistically significant decreases in whole blood lactate and core–peripheral temperature difference, and increases in mean arterial pressure and urine volumes. In non-survivors at the same stage in resuscitation the only significant change was a small increase in urine volume.

In the survivors after 24 h of resuscitation, the trend of haemodynamic and metabolic improvement was confirmed. By this time eight of the non-survivors had died, and in the other seven haemodynamic and metabolic values remained poor.

These data suggest that whole blood lactate measurement can be used to assess prognosis after 3 h of resuscitation in severely shocked patients, but in this respect does not offer advantages over conventional haemodynamic measurements.

REFERENCE

Ruiz, C. E., Weil, M. H., and Carlson, R. W. (1979). *J.A.M.A.*, 242, 165.

TABLE III. *Lactate and haemodynamic changes measured on admission to I.C.U. and 3 and 24 h later (mean ± SEM).* *$P < 0.01$ *from admission value.* †n = 7

| | Time of measurements (h) | | |
|---|---|---|---|
| | 0 | 3 | 24 |
| Survivors ($n$ = 15) | | | |
| Lactate (mmol litre$^{-1}$) | 4.39 ± 0.73 | 3.22 ± 0.43* | 2.04 ± 0.22* |
| Mean art. pressure (mm Hg) | 58.20 ± 3.1 | 78.80 ± 3.3* | 82.10 ± 3.0* |
| Urine volume (ml h$^{-1}$) | 22.80 ± 3.0 | 80.70 ± 10.6* | 76.30 ± 9.4* |
| Core–periph. temp. diff. (°C) | 9.80 ± 1.1 | 5.90 ± 0.9* | 3.20 ± 0.5* |
| Non-survivors ($n$ = 15) | | | |
| Lactate (mmol litre$^{-1}$) | 4.95 ± 0.90 | 4.98 ± 0.90 | 4.13 ± 1.50† |
| Mean art. pressure (mm Hg) | 59.20 ± 2.5 | 58.30 ± 2.1 | 54.30 ± 4.1† |
| Urine volume (ml h$^{-1}$) | 20.20 ± 4.0 | 27.90 ± 7.3* | 33.30 ± 14.8† |
| Core–periph. temp. diff. (°C) | 9.90 ± 0.7 | 9.00 ± 0.8 | 6.70 ± 1.9† |

## HALOTHANE ANAESTHESIA CHANGES THE EARLY COMPONENTS OF THE AUDITORY EVOKED RESPONSE IN MAN

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This study examined the effect of halothane anaesthesia on the auditory evoked response, derived from the electroencephalogram (e.e.g.), in response to a click stimulus. These early components of this response (also referred to as the brainstem and middle latency potentials) are thought to originate from precise anatomical locations within the auditory pathway (Maurer, Leitner and Schafer, 1980). Consequently they may be used to detect the site of action and possible graded effects of anaesthetics within the auditory pathway. The characteristic brainstem response (0–8 ms) is represented by a series of well-defined peaks labelled I–VI and the middle latency (8–50 ms) by peaks labelled No, Po, Na, Pa, Nb (Picton et al., 1974).

Six patients (ages 20–43 yr) were studied. Anaesthesia was induced with thiopentone 2–4 mg kg$^{-1}$ and the trachea intubated following the administration of pancuronium 0.1 mg kg$^{-1}$. Anaesthesia was maintained with nitrous oxide and oxygen for 5 min. Halothane was added in 0.5% increments at 10-min intervals to achieve an end-tidal halothane concentration of approximately 1%, measured using a mass spectrometer. Mechanical ventilation was adjusted continuously to maintain end-tidal carbon dioxide at approximately 4.5%.

The e.e.g. was recorded before anaesthesia and continuously during the induction and maintenance of anaesthesia, whilst a click stimulus (repetition rate 6 s$^{-1}$) was applied via headphones. The auditory evoked response was derived for a pre-anaesthetic period and for each increment of halothane. Values for the latencies and amplitudes of peaks III, V, Pa and Nb were obtained.

Regression analyses were performed of the amplitudes and latencies of peaks III, V, Pa, Nb on end-tidal halothane concentration. The latencies increased and the amplitudes decreased with end-tidal halothane concentration. For each peak a common slope for the six subjects was calculated and its significance from zero tested. Significant regressions were obtained for the latencies of the four peaks III, V, Pa, Nb ($P < 0.01$, 0.001, 0.001, 0.05 respectively) and for the amplitudes of Pa and Nb ($P < 0.01$, 0.05 respectively).

The effect of anaesthetics on the middle latency potentials has received little attention. The brainstem potentials are generally considered resistant to c.n.s. depressants. Duncan, Sanders and McCullough (1979) were unable to demonstrate an effect of halothane on the brainstem components. However, we have shown a graded response on the latencies of the brainstem and the latencies and amplitude of the middle latency components during anaesthesia.

### REFERENCES

Duncan, P. G., Sanders, R. A., and McCullough, D. W. (1979). *Can. Anaesth. Soc. J.*, **26**, 492.

Maurer, K., Leitner, H., and Schafer, E. (1980). In *Evoked Potentials*, p. 391. Lancaster: M.T.P. Press.

Picton, T. W., Hillyard, S. A., Krausz, H. I., and Galambos, R. (1974). *Electroenceph. Clin. Neurophysiol.*, **36**, 179.

## HAEMODYNAMICS OF VERAPAMIL DURING ENFLURANE ANAESTHESIA

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Verapamil is used increasingly for the treatment of supraventricular tachyarrhythmias, hypertrophic cardiomyopathy, hypertension and angina, especially where coronary artery spasm is a component of restriction to myocardial perfusion (Stone et al., 1980). In these situations, verapamil acts by altering calcium flux at cellular level, and its negative inotropic effects are well recognized. Halogenated anaesthetics have a direct negative inotropic effect and also alter calcium ion binding at cellular level (Ohnishi et al., 1980). There is little information on the interactions of verapamil and enflurane anaesthesia. Therefore, the combined effects of the two agents on global and regional myocardial function have been investigated.

Eight dogs, premedicated with morphine 0.5 mg kg$^{-1}$, and under halothane anaesthesia, were instrumented for measurement of e.c.g., aortic and left ventricular pressure and aortic flow, following left lateral thoracotomy. Shortening in two areas of left ventricular wall (supplied by left anterior descending and left circumflex coronary arteries) was measured with miniature ultrasonic crystals implanted at subendocardial level (Lowenstein et al., 1981). Left ventricular $dP/dt_{max}$, aortic acceleration and stroke volume were derived electronically. The animals were ventilated with 60% oxygen in nitrogen ($V_T$ 40 ml kg$^{-1}$) and carbon dioxide added to maintain 5.2% end-tidal carbon dioxide.

After completion of the surgical preparation, 1.8% enflurane was substituted for halothane, and the preparation allowed to stabilize for 1 h. The haemodynamic responses to cumulative incremental doses of verapamil 0.01–0.32 mg kg$^{-1}$, injected into the pulmonary artery, were observed.

Observations made 5 min after verapamil challenge are reported. Compared with control (paired Student's *t* test), at the highest dose of verapamil, the changes in mean arterial pressure (10% reduction), cardiac output (16% reduction) or systemic vascular resistance (15% increase) were not significant. There were dose-dependent reductions in LV $dP/dt_{max}$ (max. 50%, $P < 0.001$), aortic acceleration (max. 54%, $P < 0.001$) and stroke volume (max. 21%, $P < 0.001$). Heart rate increased progressively to a maximum of 14% ($P < 0.05$). After verapamil 0.32 mg, LVEDP increased by 2 mm Hg ($P < 0.05$). Modest increases in maximum systolic length (max. 8%) were accompanied by a dose-dependent reduction in systolic shortening (max. 41%, $P < 0.01$ both segments).

Although verapamil and enflurane produced a marked depression of contractility (LV $dP/dt$, aortic acceleration and systolic shortening) cardiac output was relatively well maintained, possibly by a reflexly mediated increase in heart rate.

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REFERENCES

Lowenstein, E., Foëx, P., Francis, C. M., Davies, W. L., Yusuf, S., and Ryder, W. A. (1981). *Anesthesiology*, 55, 349.

Ohnishi, S. T., DiCamillo, C. A., Singer, M., and Price, H. L. (1980). *J. Cardiovasc. Pharmacol.*, 2, 67.

Stone, P. H., Antman, E. M., Muller, J. E., and Braunwald, E. (1980). *Ann. Int. Med.*, 93, 886.

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## PERIPHERAL VASCULAR EFFECTS OF ENFLURANE AND HALOTHANE

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Enflurane is reported to reduce systemic vascular resistance to a greater extent than halothane, and this may contribute to reduction of arterial pressure (Kaplan, Miller and Bailey, 1976). Although Bennett and colleagues (1977) reported that the addition of nitrous oxide to enflurane anaesthesia caused an increase in peripheral vascular resistance, this was not confirmed by Smith and others (1978). In the present study the peripheral vascular effects of equipotent concentrations of 3.4% enflurane and 1.5% halothane were compared before surgery using venous occlusion plethysmography.

Anaesthesia was induced with thiopentone 5 mg kg$^{-1}$. Heart rate (HR), arterial pressure (AP), forearm blood flow (FBF) and forearm vascular resistance (FVR) were measured in 60 healthy unpremedicated patients allocated to three groups of 20. Plasma catecholamine concentrations were measured in 10 patients before and after the addition of nitrous oxide. All measurements were made following 10 min periods of stable anaesthesia.

*Group 1.* The addition of either volatile agent to stable nitrous oxide–oxygen anaesthesia produced minimal increases in FBF, but because of substantial decreases in AP (E, −18%; H, −11%), FVR was reduced significantly, especially with enflurane ($P < 0.02$). HR was reduced significantly with halothane ($P < 0.001$), but enflurane produced little change.

*Group 2.* When 67% nitrous oxide was added to halothane in 100% oxygen, HR was significantly reduced ($P < 0.01$), FBF significantly decreased ($P < 0.001$), and FVR significantly increased ($P < 0.01$). These changes did not occur with enflurane.

*Group 3.* When 67% nitrous oxide was substituted for nitrogen, comparable changes occurred with both anaesthetics: there were significant reductions in HR (E, $P < 0.01$; H, $P < 0.001$), FBF was significantly decreased (E, $P < 0.05$; H, $P < 0.01$) and there were significant increases in FVR (E, $P < 0.05$; H, $P < 0.001$).

Measurements of plasma catecholamine concentrations before and after the addition of nitrous oxide showed no significant changes. Enflurane produced consistently greater $Pa_{CO_2}$ values than halothane (E, 7.19 kPa; H, 6.34 kPa).

During enflurane anaesthesia, FVR is reduced substantially and it is reasonable to assume that this vasodilatation contributes to the hypotensive effect of the agent. Consistent increases in FVR and decreases in HR follow the addition of nitrous oxide to halothane anaesthesia. Inspired oxygen concentration ($FI_{O_2}$) appears to be an important factor in determining the response of the peripheral circulation to the addition of nitrous oxide. When it is added to halothane, increases in FVR occur at both low (0.33) and high (1.0) $FI_{O_2}$ values, whereas with enflurane these changes only happen when the lower $FI_{O_2}$ is being inhaled. Catecholamine concentrations suggest that this response is not a result of increased sympathetic activity. Observations of $Pa_{CO_2}$ confirm that enflurane has a slightly greater respiratory depressant effect than halothane in the absence of surgery, but does not produce recordable increases in plasma catecholamine concentrations.

REFERENCES

Bennett, G. M., Loeser, E. A., Kawamura, R., and Stanley, T. H. (1977). *Anesthesiology*, 46, 227.

Kaplan, J. A., Miller, E. D., and Bailey, D. R. (1976). *Anesth. Analg. (Cleve.)*, 55, 263.

Smith, N. T., Calverley, R. K., Prys-Roberts, C., Eger, E. I., and Jones, C. W. (1978). *Anesthesiology*, 48, 345.

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## THE NEUROMUSCULAR BLOCKING ACTION OF ATRACURIUM IN THE DOG

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Atracurium besylate is a new non-depolarizing muscle relaxant, the elimination of which is independent of both the liver and the kidney. The pharmacology of the drug has been described (Hughes and Chapple, 1981).

If was found that a dose of 0.25 mg kg$^{-1}$ was required to produce total neuromuscular blockade in the dog as assessed by single twitch and tetanic responses of the gastrocnemius muscle. The time to full recovery was 43 min for single twitch and 56 min for tetanic response.

The investigations were carried out in four mature labrador dogs and the technique used was similar to that described previously (Cullen, Jones and Snowdon, 1980). After premedication with acepromazine 0.1 mg kg$^{-1}$ and atropine 0.044 mg kg$^{-1}$ anaesthesia was induced with thiopentone 22 mg kg$^{-1}$ and the trachea intubated.

Anaesthesia was maintained with nitrous oxide and oxygen 2 : 1 and ventilation was controlled using a type of Mapleson E circuit (Lamplugh, Jones and Snowdon, 1979). The animals were maintained in a state of moderate hyperventilation with $Pa_{CO_2}$ approximately 35 mm Hg. $Pa_{CO_2}$ was controlled by adjusting the fresh gas flow to the circuit by reference to the arterial blood-gas values. The dogs were placed in left lateral recumbency and the left foreleg was fixed in a padded wooden clamp. The left ulnar nerve was stimulated at the elbow using steel needle electrodes. Square wave stimuli of 0.3 ms duration were delivered from a Grass stimulator (S8). The voltage was adjusted to 20% above that which was required to produce a supramaximal response. Train-of-four stimuli of frequency 2 Hz were applied and repeated at a frequency of 0.1 Hz. The mechanical response was monitored by attaching a Grass force displacement transducer (FTO3) to the foot and recording the signal on a Devices two-channel recorder.

A control recording was obtained before the administration of the atracurium. The drug was administered into a rapidly running drip of normal saline inserted into the cephalic vein of the right forelimb. Doses of atracurium 0.2, 0.4 and 0.6 mg kg$^{-1}$ were used. At the point when the twitch height of the first of the four stimuli returned to 50% of its original height atropine 0.6 mg was administered. This was followed 1 min later by atropine 0.6 mg with neostigmine 2.5 mg and again 1 min later by a second dose of neostigmine 2.5 mg. The observations were repeated once in each dog for each of the three doses at intervals of not less than 1 week.

The increase in dosage was associated with a decreased time of onset of neuromuscular block, the times being 2.7 min (range 2.17–3.00) at 0.2 mg kg$^{-1}$, 1.6 min (range 1.33–2.66) at 0.4 mg kg$^{-1}$ and 1.5 min (range 1.0–2.0) at 0.6 mg kg$^{-1}$; the difference between the first two times (but not between the second and third) was significant ($P < 0.001$).

Increase in dosage was associated also with an increased duration of action: the times to full reversal from the time of administration of atracurium were 20 min (range 14.0–32.4) 0.2 mg kg$^{-1}$, 31 min (range 20.3–39.1) 0.4 mg kg$^{-1}$ and 47 min (range 34.5–66.7) 0.6 mg kg$^{-1}$. In this instance, the difference between first and second times mentioned and between second and third are statistically significant.

REFERENCES

Cullen, L. K., Jones, R. S., and Snowdon, S. L. (1980). *Br. Vet. J.*, **136**, 154.

Hughes, R., and Chapple, D. J. (1981). *Br. J. Anaesth.*, **53**, 31.

Lamplugh, G., Jones, R. S., and Snowdon, S. L. (1979). *J. Small Anim. Pract.*, **20**, 557.

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## INITIAL CLINICAL EXPERIENCES WITH ORG NC45: A COMPETITIVE MYONEURAL BLOCKING AGENT

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The new myoneural blocking agent Org NC45 (Crul and Booij, 1980) has been evaluated in clinical use in 140 healthy adult patients undergoing elective surgery. Intubating conditions at predetermined times, onset of myoneural block, duration of action, effects on heart rate and arterial pressure and the quality of reversal of paralysis were all assessed.

Premedication and induction of anaesthesia were standardized with diazepam 10 mg orally and thiopentone 5 mg kg$^{-1}$ respectively, while anaesthesia was maintained with nitrous oxide and oxygen, supplemented with inhalation agents or neuroleptanaesthesia.

Intubation conditions were assessed at predetermined times according to the scheme of Lund and Stovner (1962) and Young, Clarke and Dundee (1975). Neuromuscular transmission was studied using a train-of-four stimulus delivered from a peripheral nerve stimulator (Myotest, Biometer Limited).

Using a 0.1-mg kg$^{-1}$ dose, intubation could be easily carried out after 90–120 s. The quality at 60 s was not significantly improved using a 0.15-mg kg$^{-1}$ dose. The time to achieve complete neuromuscular block and the duration of action are given in table IV. The duration of action of each subsequent increment of Org NC45 was approximately the same, thus showing a lack of cumulation. Heart rate and rhythm and arterial pressure were stable during anaesthesia. Recovery of nuromuscular transmission was prompt following anticholinesterase administration.

Table IV. *Time to 100% block and duration of action following two doses of Org NC45. The figures in brackets indicate the number of patients studied using a peripheral nerve stimulator*

| Dose (mg kg$^{-1}$) | Number of patients | Time to onset of 100% block (s) | Mean duration to 75% block (min ± SEM) | |
|---|---|---|---|---|
| | | | Fentanyl droperidol | Halothane enflurane |
| 0.10 | 80 (44) | 245 | 23 ± 0.76 | 34 ± 2.11 |
| 0.15 | 60 (28) | 162 | 36 ± 1.90 | 49 ± 5.27 |

REFERENCES

Crul, J. F., and Booji, L. H. D. J. (1980). *Br. J. Anaesth.*, **52**, 49S.

Lund, I., and Stovner, J. (1962). *Acta Anaesthesiol. Scand.*, **6**, 85.

Young, H. S. A., Clarke, R. S. J., and Dundee, J. W. (1975). *Anaesthesia*, **30**, 30.

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## PRELIMINARY STUDIES IN MAN WITH PIPECURIUM BROMIDE (ARDUAN), A NEW STEROID NEUROMUSCULAR BLOCKING AGENT

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Pipecurium bromide (Arduan) is a new steroid neuromuscular blocking agent which has undergone clinical trials in Hungary (Boros et al., 1980). These studies indicate that it has a potency similar to that of pancuronium bromide, with the same, or slightly longer, duration of action, and minimal cardiovascular effects (Barankay, 1980; Bunjatjan and Miheev, 1980).

We have investigated this drug in nine healthy patients (ASA grade I or II) undergoing gynaecological surgery. Cardiovascular effects were also studied in a further 10 patients (ASA I or II) in whom a radial artery and central venous catheter had been inserted for major oncological surgery. The patients' ages ranged from 25 to 55 yr. The isometric single twitch response of the adductor pollicis was measured in all patients in response to 0.2 ms supramaximal stimulation at 0.1 Hz of the ulnar nerve at the wrist.

In the nine gynaecological patients estimation of the 50% blocking dose (ED$_{50}$) and the 95% blocking dose (ED$_{95}$) was made by the addition of incremental doses of 0.02 mg kg$^{-1}$ initially and 0.01 mg kg$^{-1}$ thereafter, on the levelling out of the twitch response.

This incremental dose response suggested an ED$_{50}$ of 0.03 mg kg$^{-1}$ (±0.007 SD) and an ED$_{95}$ of 0.05 mg kg$^{-1}$ (±0.009 SD) during neuroleptanaesthesia.

On the basis of these results, a dose of 0.05 mg kg$^{-1}$ was used as a single bolus in the patients with invasive monitoring. Five patients received 0.5–1% halothane and five received neuroleptanaesthesia. Suxamethonium was used for endotracheal intubation, and more than 20 min was allowed to elapse before administration of pipecurium. In all 10 patients, complete block of the adductor pollicis twitch was achieved and during the 10 min following the bolus injection no changes ($<5\%$) were seen in heart rate, arterial or central venous pressure.

In seven patients the block was allowed to recover spontaneously following the initial dose; in the remainder one-quarter of the initial dose was given at between 15% and 25% recovery and repeated to maintain surgical relaxation.

All patients received neostigmine 2 mg at the end of surgery, and a satisfactory reversal of block occurred.

The results (table V) are similar to the findings of previous authors and suggest that pipecurium merits further investigation for use in long surgical procedures.

TABLE V. *Neuromuscular effects of pipecurium bromide 0.05 mg kg$^{-1}$, halothane and neuroleptanaesthesia (NLA) (mean ± SD; range in parentheses)*

| | Anaesthesia | |
|---|---|---|
| Time to max. block (min) | 2.45 ± 0.67<br>(1.5–3.0) ($n = 5$) | 2.05 ± 0.53<br>(1.5–2.5) ($n = 5$) |
| Time max. block to 25% recovery (min) | 45.0 ± 29.2<br>(26–80) ($n = 5$) | 52.5 ± 29.5<br>(32–96) ($n = 5$) |
| Recovery time (25–75% block) (min) | 29.0 ± 12.7<br>(20 ± 48) ($n = 4$) | 26.3 ± 4.0<br>(22–30) ($n = 3$) |

REFERENCES

Barankay, A. (1980). *Arzneim. Forsch./Drug Res.*, **30**, 386.

Boros, M., Szenohradsky, J., Marosi, G., and Toth, I. (1980). *Arzneim. Forsch./Drug Res.*, **30**, 389.

Bunjatjan, A. A., and Miheev, V. I. (1980). *Arzneim. Forsch./Drug Res.*, **30**, 383.

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## IDENTIFICATION OF INTERACTING DYNAMIC EFFECTS ON MUSCLE PARALYSIS USING ETHRANE IN THE PRESENCE OF PANCURONIUM

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The potentiating effect of inhalation anaesthetic agents such as halothane and Ethrane on pancuronium-induced muscle paralysis has been reported (Stanski et al., 1980). This work is a quantitative evaluation of the effect using enflurane in the presence of pancuronium. This quantitative measurement has been made possible using the techniques of automatic feedback control (Brown et al., 1980) and identification methods based on PRBS testing (Linkens, Rimmer and Asbury, 1981).

The measurements were made on healthy mongrel dogs. Anaesthesia was induced i.v. with methohexitone 5 mg ml$^{-1}$ and maintained using a constant infusion of droperidol 0.4 mg kg$^{-1}$ h$^{-1}$ and fentanyl 6 µg kg$^{-1}$ h$^{-1}$. Automatic ventilation with oxygen in air was used throughout the experiments and the tidal volume adjusted to maintain an end-exhaled carbon dioxide concentration of 4%. At the conclusion of the experiments the residual effects of the neuromuscular blocker were reversed using neostigmine. Muscle blockade was measured by an evoked e.m.g. from the forelimb muscles and pancuronium was infused i.v. using a peristaltic pump. Enflurane was administered using a standard Cyprane vaporizer, and the enflurane concentrations in expired gases were measured with a mass spectrometer (type Medishield Multi-gas Analyser MS2).

The experiments have quantified both steady-state consumption and transient dynamic interactive effects. For steady-state conditions the trial was initiated under closed-loop control until a specified paralysis (usually 70%) has been achieved in the absence of enflurane. Drug consumption was measured directly as a burette reading, and indirectly as peristaltic pump voltage. Enflurane at a given concentration was then introduced and the closed-loop allowed to resettle to the correct paralysis level (the integral action in the controller removes offset completely). Drug consumption was then remeasured, with the resulting change giving a quantitive indication of potentiation. This procedure was repeated for enflurane concentrations of 0–3%, in three dogs, and a potentiating effect was observed.

In these trials when the enflurane concentration was changed in a step-wise manner the e.m.g. signal representing the output of the closed-loop feedback system showed a transient oscillation characteristic of disturbance dynamics. To identify these dynamics, PRBS tests have been applied to the open-loop system. To undertake PRBS identifications the blockade was maintained initially under closed-loop control to 70%, and then the loop opened with the infusion rate set manually to the steady state closed-loop consumption. A PRBS signal was then used to perturb the enflurane vaporizer between 0% and 3%. A bit interval of 33.3 s and sequence length of 128 were used. The resulting e.m.g. signal was logged and subsequently analysed with an identification package (SPAID). The dynamic model obtained showed a small time delay in the order of 10 s and two time constants of about 35 s and 12 min. The dynamics are similar to those of the pancuronium model, and thus feed-forward control to remove enflurane disturbances would be difficult. It is likely, however, that halothane will have slower dynamics, in which case feedforward disturbance control would become feasible.

REFERENCES

Brown, B. H., Asbury, A. J., Linkens, D. A., Perks, R., and Anthony, M. (1980). *Clin. Phys. Physiol. Meas.*, **1**, 203.

Linkens, D. A., Rimmer, S. J., and Asbury, A. J. (1981). *Br. J. Anaesth.*, **53**, 859.

Stanski, D. R., Ham, J., Miller, R. D., and Scheiner, L. B. (1980). *Anesthesiology*, **52**, 483.

*Br. J. Anaesth.* (1982), 54, 791

# CORRESPONDENCE

## HUMIDITY AND COMPRESSORS

Sir,—I refer to the paper by Conely, Railton, and MacKenzie (1981) about ventilator problems caused by humidity in the air supplied from simple compressors. While simple compressors deliver fully saturated air, I disagree with their conclusion that medical air must be used. There are air compressors on the market that incorporate a condensation removal system which allows one to use the compressor with a ventilator without worry about the problems noted in the article.

If these gentlemen would wish to perform an additional study of compressors with condensation removal systems, I would be more than happy to arrange the loan of a unit manufactured by my employer, Timeter Instrument Corporation, for that study. I believe that they would find the other manufacturers of such devices equally cooperative.

DAVID S. PRYCE
*Export Sales Manager,*
*Trimeter Instrument Corporation,*
*Lancaster PA U.S.A.*

### REFERENCE

Conely, J. I. M., Railton, R., and MacKenzie, A. I. (1981). Ventilator problems caused by humidity in the air supplied from simple compressors. *Br. J. Anaesth*, 53, 549.

## AIR EMBOLISM IN THE SITTING POSITION

Sir,—Drs Gilsanz and Avello (1982) recommend the use of PEEP up to 10 cm during operations in the sitting position. This degree of end-expiratory pressure can be expected to increase mean central venous pressure only to some 5 cm $H_2O$. This increase is quite insufficient to fill the veins in the upper part of the neck and sub-occipital region. While providing some false comfort to the anaesthetist, I do not believe this practice would significantly reduce the frequency of air embolism.

MERLIN MARSHALL
*Newcastle upon Tyne*

### REFERENCE

Gilsanz, F. J., and Avello, F. (1982). Positive end-expiratory pressure and air embolism in the sitting position. *Br. J. Anaesth.*, 54, 110.

## SODIUM NITROPRUSSIDE AND CYANIDE RELEASE

Sir,—Bisset and colleagues (1981) have recently claimed that the cyanide (HCN) reported to be present in the blood of patients and animals receiving infusions of sodium nitroprusside (SNP) is a product of photolysis during infusion or the assay procedure, or both. This claim carries serious implications. If they are correct then a large number of workers have been badly misled and their scientific expertise is called into question. If incorrect, then the suggestion that "it may be safe to infuse quantities larger than those currently recommended" will endanger patients' lives, if implemented. We believe that the statement "that there is, to date, no unambiguous evidence that cyanide is released from SNP *in vivo*" is incorrect for the following reasons:

*(A) Is cyanide a product of the action of light on the infusion solution?*

(i) We have shown (Vesey and Batistoni, 1977) that very little photolysis occurs when infusion solutions of SNP are exposed to diffuse light, either artificial or daylight, for short periods during hypotensive anaesthesia. Significant breakdown of the compound was found only following exposure to diffuse light for many hours or after the action of direct sunlight for a short time.

(ii) Injection of bolus doses of SNP (with very little exposure of the solution to light) to dogs, resulted in a more protracted increase and decrease of blood HCN concentrations than after bolus doses of equivalent amounts of KCN (Vesey et al., 1979). This demonstrates that SNP breaks down to release HCN *in vivo* at a finite rate and that the HCN found in the blood is not introduced as free cyanide in the infusion solution.

*(B) Is cyanide produced during the assay procedure?*

(i) No experimenter "worth his salt" would measure the free HCN present in blood fractions containing nitroprusside ($Na_2Fe(CN)_5NO$) without first determining whether cyanide could arise artefactually during his assay procedure. At the outset of our studies we established that HCN was not released from SNP during the assay under normal laboratory lighting conditions. The aeration technique we use to isolate and concentrate the HCN from blood samples etc. (Vesey, Cole and Simpson, 1976a) requires the addition of three volumes of 10% trichloroacetic acid to plasma or haemolysed red cells to give a pH $<1.5$ (not pH 4.0 as Bisset and colleagues appear to have used). Although quoting from our paper (Vesey and Batistoni, 1977) that infusion solutions of SNP exposed to sunlight were 45% decomposed in 2 h Bisset and others (1981) failed to mention that, before exposure to sunlight, no HCN was detectable in the SNP solutions whilst using our aeration procedure. This demonstrates that HCN is not liberated during the assay. We would not argue with the fact that aquapentacyanoferrate ($(Fe(CN)_5H_2O)^{2-}$) may be formed on exposure of SNP solutions to strong light and would release HCN on acidification. However, since $OH^-$ is necessary, this change in the molecule is unlikely to occur in the strongly acid conditions used in our assay procedure, although certainly one would expect it to occur more readily at pH 4.0 and with the light of a 100-W bulb directed on to the aeration mixture (Bisset et al., 1981).

(ii) We have also shown (Vesey and Krapez, 1980) that when blood is incubated with SNP at 37 °C in foil-wrapped tubes and samples removed at timed intervals for analysis, while little HCN is present in the initial sample, the amount of HCN increases with time of incubation. If cyanide is released on assay then one would expect the amount of HCN to be the same for each sample and independent of time.

(iii) Incubation work suggests that the reaction of SNP with blood is slow, 50% of the available HCN being released in 20 min and $>90\%$ in 2 h (Vesey, Cole and Simpson, 1976b). The addition of acid to a mixture of SNP and blood without prior incubation, as Bisset and others appear to have done, would not be expected to yield significant amounts of HCN on immediate analysis, particularly if measured with the relatively insensitive cyanide specific electrode. The statement that there are no *in vitro* reactions, apart from photolysis, that result in the release of HCN from SNP (Bisset et al., 1981) is incorrect. Rock and Swinehart (1966) suggest, that following reaction of SNP with sulphides, cyanide can be released under certain conditions. Indeed we have found the HCN is obtained after incubation with cysteine at pH 7.4 (Vesey, Cole and Simpson, 1976b).

(iv) A recent patient infused with SNP 1.3 g over the course of 108.5 h for ergot poisoning, showed an increase of plasma thiocyanate (SCN; a detoxication product of HCN) from 79 µmol litre$^{-1}$ to 850 µmol litre$^{-1}$ (unpublished data). Any effect of light on the SNP was eliminated since both the infusion solution and the giving set were foil-wrapped. This confirms that SNP breaks down to release HCN *in vivo* (and not during the assay), not only because we are able to measure increased concentrations of HCN in the blood of patients and animals infused with SNP, but also because plasma SCN concentrations increase as a result of the detoxication of endogenously produced cyanide.

For these reasons we do not believe that the paper of Bisset and colleagues presents a valid alternative explanation for the many independent reports of increased concentrations of cyanide and its products in blood following infusions of SNP. We would therefore urge that maximum dosage recommendations be strictly adhered to.

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REFERENCES

Bisset, W. I. K., Butler, A. R., Glidewell, C., and Reglinski, J. (1981). Sodium nitroprusside and cyanide release: reasons for re-appraisal. *Br. J. Anaesth.*, 53, 1015.

Rock, P. A., and Swinehart, J. H. (1966). The kinetics of aqueous hydrogen sulphide–nitroprusside system. *Inorg. Chem.*, 5, 1078.

Vesey, C. J., and Batistoni, G. A. (1977). The determination and stability of sodium nitroprusside in aqueous solutions. *J. Clin. Pharm.*, 2, 105.

—— Cole, P., and Simpson, P. (1976a). Cyanide and thiocyanate concentrations following sodium nitroprusside infusion in man. *Br. J. Anaesth.*, 48, 651.

—— —— —— (1976b). Changes in cyanide concentrations induced by sodium nitroprusside. *Br. J. Anaesth.*, 48, 268.

—— Krapez, J. R. (1980). The effects of sodium nitroprusside and cyanide on haemoglobin function. *J. Pharm. Pharmacol.*, 32, 256.

—— Simpson, P. J., Adams, L., and Cole, P. V. (1979). Metabolism of sodium nitroprusside and cyanide in the dog. *Br. J. Anaesth.*, 51, 89.

Sir,—Dr Vesey and his colleagues criticize our conclusion that cyanide is released from nitroprusside, not by reaction with blood, but via the photoproduct aquapentacyanoferrate(III), $[Fe(CN)_5H_2O]^{2-}$. When we started this research we were looking for a mechanism for the blood-induced breakdown of nitroprusside and it was only after several years' work, during which we were unable to observe this reaction, that we began to question the suitability of the analytical procedure used by previous workers. We now believe that the previously accepted hypothesis that cyanide is released by reaction of nitroprusside with haemoglobin (Smith and Kurszyna, 1974) is inconsistent with the known properties of the nitroprusside ion, is inconsistent with the laws of thermodynamics, and has been specifically disproved (Bisset et al., 1981). Since the chemistry has plainly not been understood by our critics we summarize it here; full chemical details are discussed in the last reference.

The nitroprusside ion $[Fe(CN)_5NO]^{2-}$ (*pace* Vesey and co-workers, it is not a molecule or a radical) has high thermodynamic stability (formation constant $\beta_5 = 10^{30}$) and contains low-spin Fe(II), $d^6$ and is, therefore, inert to ligand substitution. Indeed, at one time the recommended antidote for cyanide poisoning was the administration of Fe(II) salts because of the formation of a very stable and inert cyanoferrate(II). Of the hundreds of papers in the chemical literature on nitroprusside known to us, none contains an unambiguous example of cyanide release under non-photochemical or non-redox conditions; the example cited (Rock and Swinehart, 1966) is speculative.

Photolysis of nitroprusside, independent of pH and wavelength, results in formation of the aqua ion $[Fe(CN)_5H_2O]^{2-}$ (Lodzinska and Gogolin, 1973; Wolfe and Swinehart, 1975). This ion is also of high thermodynamic stability, $\beta_5 = 10^{36}$, *but* contains low-spin Fe(III), $d^5$, and is, therefore, readily susceptible to ligand substitution. This means that the cyanide ligands of the aqua ion can be displaced by other ligands. The conditions of the analytical procedure of Vesey and co-workers are ideally constructed to do just that. The solution is acidified and aerated. Any cyanide released by ligand exchange with water is protonated to give volatile HCN and swept out of the solution. This is a non-equilibrium, entropy-driven process. It is essential always to be clear whether reactions are proceeding under equilibrium or non-equilibrium conditions, as this is crucial to the yield of HCN observed. From the analytical point of view it means that, if the nitroprusside solution is at any time exposed to light, before infusion or mixing, during incubation, or during analysis, it is inevitable that cyanide will be detected. The absence or presence of blood is irrelevant. The amount of cyanide will depend upon the radiant power to which the solution is exposed, but we hope our critics will concede that this particular analytical procedure is peculiarly ill-suited for the detection of cyanide in the presence of nitroprusside. We have never suggested that cyanide is directly generated by the action of light on nitroprusside. In our hands the use of a more selective analytical technique, as ion-sensitive electrode, provided no evidence for cyanide release on mixing, and incubating, nitroprusside with different blood fractions as well as whole blood; we note that Vesey and colleagues ignore our clear statement that we obtained the same results using the more sensitive colorimetric assay.

Vesey and colleagues are seriously in error when they state that hydroxide is necessary for the formation of the ion $[Fe(CN)_5H_2O]^{2-}$. The action of hydroxide on nitroprusside produces a totally different ion, $[Fe(CN)_5H_2O]^{3-}$,—an Fe(II) species which is entirely irrelevant to the present discussion. An appreciation of metal oxidation states is crucial to an understanding of these iron complexes.

Most non-redox reactions of nitroprusside involve attack on the nitrosyl group and the $Fe(CN)_5$ moiety remains intact. The complete breakdown of nitroprusside to give cyanide, under ambient, equilibrium conditions is, because of its high $\beta_5$ value, an astonishing reaction; the laws of thermodynamics are not suspended, even *in vivo*.

From well-founded chemical considerations we have criticized the analytical procedure used by previous workers for the assay of cyanide in the presence of nitroprusside. Until these criticisms are answered satisfactorily all *in vivo* or *in vitro* experiments purporting to confirm cyanide release by reaction with blood must, we believe, receive the old Scottish legal verdict of not proven. If cyanide is indeed liberated as readily *in vivo* as Vesey and co-workers have repeatedly asserted, we question whether its use in clinical practice should continue.

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REFERENCES

Bisset, W. I. K., Burdon, M. G., Butler, A. R., Glidewell, C., and Reglinski, J. (1981). Photochemistry of the nitroprusside ion and the consequences for the detection of cyanide in mixtures of nitroprusside and blood: use of nitroprusside as a hypotensive agent. *J. Chem. Res.* (S), **299**, 3501.

Lodzinska, A., and Gogolin, R. (1973). Effect of pH on photolysis of sodium pentacyanonitrosylferrate in aqueous solutions. *Rocz. Chem.*, **47**, 1101.

Rock, P. A., and Swinehart, J. H. (1966). The kinetics of the aqueous hydrogen sulphide-nitroprusside system. *Inorg. Chem.*, **5**, 1078.

Smith, R. P., and Kruszyna, H. (1974). Nitroprusside produces cyanide poisoning *via* a reaction with haemoglobin. *J. Pharmacol. Exp. Ther.*, **191**, 557.

Wolfe, S. K., and Swinehart, J. H. (1975). Photochemistry of pentacyanonitrosylferrate(2-), nitroprusside. *Inorg. Chem.*, **14**, 1049.

## ANTAGONISM OF NEUROMUSCULAR BLOCK

Sir,—The recent discussion between Foldes (1981) and Payne and Hughes (1981) regarding the way atropine and neostigmine should be administered to antagonize neuromuscular block has prompted us to write this letter.

Macintosh (1949) and Clutton-Brock (1949) described patients in whom cardiac arrests occurred when atropine and neostigmine were given together. These and the comments by Bain and Broadbent (1949) are given as reasons by Drs Payne and Hughes for advocating administration of atropine before neostigmine. However, closer scrutiny of these reports shows administration of reversal mixtures containing only 1/100 gr (0.65 mg) of atropine with neostigmine 2–2.5 mg during a cyclopropane anaesthetic, with apparently unassisted respiration during reversal. It was pointed out by Hunter (1953) and Edwards and his colleagues (1956) that 1/100 gr (0.65 mg) of atropine was inadequate and the former showed that atropine 1.3 mg was required with each 2.5 mg of neostigmine. A recent study (Mirakhur et al., 1981) has actually showed that even atropine $20\ \mu g\ kg^{-1}$ (1.2 mg in a 60-kg patient) might be inadequate whether given before or in a mixture with neostigmine $50\ \mu g\ kg^{-1}$ (3.0 mg in a 60-kg patient). Bain and Broadbent (1949) also reason that, since atropine given s.c. can produce initial slowing of heart rate, the same may happen on i.v. administration. In addition, according to Bain and Broadbent the peripheral effects of atropine may commence after 20–30 min. No anaesthetist believes that i.v. atropine takes 20–30 min to produce an effect on the heart rate. Whereas initial slowing results after s.c. or i.m. administration of small to moderate doses, i.v. administration in anaesthetized patients always leads to an increase in heart rate (Eger, 1962; Mirakhur, Jones and Dundee, 1981.

More recent reports suggest that a dose of atropine in the region of 1.2 mg administered before or with neostigmine was safe provided ventilation was maintained (Riding and Robinson, 1961; Kemp and Morton, 1962; Baraka 1968a, b). They showed that, even in a mixture, the effect of atropine in increasing the heart rate appeared before the negative chronotropic effect of neostigmine. Pooler (1957) reported a patient having frightening tachycardia when given atropine before neostigmine reversal and he believed that atropine may have been responsible for unexplained deaths during reversal.

When atropine is routinely administered before neostigmine the degree of tachycardia is invariably much more than when the two drugs are given together (Baraka, 1968a, b; Ovassapian, 1969; Rosner, Kepes and Foldes, 1971; Mirakhur et al., 1981). It is even more important in ill patients with poor cardiac function not to increase their heart rates and rate–pressure products unduly—situations which are avoided by administering atropine and neostigmine together or perhaps using glycopyrrolate instead of atropine in the mixture (Cozanitis et al., 1980; Mirakhur et al., 1981).

Better understanding of the need to maintain proper ventilation during reversal has resulted in the reversal of neuromuscular block being a safe procedure.

In conclusion, we believe that atropine and neostigmine are better administered together unless there is pre-existing bradycardia of sufficient severity to warrant prior administration of the anticholinergic drug. This appears to be the current practice of the majority of anaesthetists in this country (Mirakhur et al., 1978).

R. S. J. CLARKE
R. K. MIRAKHUR
*Belfast*

REFERENCES

Bain, W. A., and Broadbent, J. L. (1949). Death following neostigmine. *Br. Med. J.*, **1**, 1137.

Baraka, A. (1968a). Safe reversal: Atropine followed by neostigmine; an electrocardiographic study. *Br. J. Anaesth.*, **40**, 27.

—— (1968b). Safe reversal: Atropine–neostigmine mixtures; an electrocardiographic study. *Br. J. Anaesth.*, **40**, 30.

Clutton-Brock, J. (1949). Death following neostigmine. *Br. Med. J.*, **1**, 1007.

Cozanitis, D. A., Dundee, J. W., Merrett, J. D., Jones, C. J., and Mirakhur, R. J. (1980). Evaluation of glycopyrrolate and atropine as adjuncts to reversal of non-depolarizing neuromuscular blocking agents in a "true-to-life" situation. *Br. J. Anaesth.*, **52**, 85.

Edwards, G., Morton, H. J. V., Pask, E. A., and Wylie, W. D. (1956). Deaths associated with anaesthesia. *Anaesthesia*, **11**, 194.

Eger, E. I. (1962). Atropine, scopolamine and related compounds. *Anesthesiology*, **23**, 365.

Foldes, F. F. (1981). Atracurium in anaesthetized man. *Br. J. Anaesth.*, **53**, 1366.

Hunter, A. R. (1953). The anticurare agents. *Br. Med. J.*, **1**, 640.

Kemp, W. W., and Morton, H. J. V. (1962). The effect of atropine and neostigmine on the pulse rates of anaesthetised patients. *Anaesthesia*, **17**, 170.

Macintosh, R. R. (1949). Death following injection of neostigmine. *Br. Med. J.*, **1**, 852.

Mirakhur, R. K., Clarke, R. S. J., Dundee, J. W., and MacDonald, J. R. (1978). Anticholinergic drugs in anaesthesia: a survey of their present position. *Anaesthesia*, 33, 133.

—— Dundee, J. W., Jones, C. J., Coppel, D. L., and Clarke, R. S. J. (1981). Reversal of neuromuscular blockade: dose determination studies with atropine and glycopyrrolate given before or in a mixture with neostigmine. *Anesth. Analg. (Cleve).*, 60, 557.

—— Jones, C. J., and Dundee, J. W. (1981). Effects of intravenous administration of glycopyrrolate and atropine in anaesthetized patients. *Anaesthesia*, 36, 277.

Ovassapian, A. (1969). Effects of administration of atropine and neostigmine in man. *Anesth. Analg. (Cleve).*, 48, 219.

Payne, J. P., and Hughes, R. (1981). Atracurium in anaesthetized man. *Br. J. Anaesth.*, 53, 1366.

Pooler, H. E. (1957). Atropine, neostigmine and sudden deaths. *Anaesthesia*, 12, 198.

Riding, J. E., and Robinson, J. S. (1961). The safety of neostigmine. *Anaesthesia*, 16, 346.

Rosner, V., Kepes, E. R., and Foldes, F. F. (1971). The effects of atropine and neostigmine on heart rate and rhythm. *Br. J. Anaesth.*, 43, 1066.

# BOOK REVIEWS

*Pediatric Anesthesia: Current Practise*, Volume 1. Edited by M. Ramez Salem. Published by Academic Press Inc. (London) Ltd. Pp. 158; indexed.

This volume, which is the first of a series planned on Pediatric Anesthesia: Current Practise, is the published transcripts of presentations given at recent paediatric anaesthetic meetings held in Chicago. The book contains 22 topics which are covered by 11 authors, some of whom have rewritten their chapters. It is obvious that other are taken verbatim from the recorded lecture. There is therefore, considerable variation in the style, presentation and content of the contributions. The topics covered range from neonatal problems including cardiovascular adaptation, prematurity, metabolic changes, fluid and electrolyte therapy and oxygen monitoring to the use of relaxants in infants, pyloric stenosis, anaesthetic considerations in patients with congenital cardiac disease for non-cardiac surgery, anaesthesia for bronchoscopy and oesophagoscopy and the bleeding tonsil. At the end of each topic there is usally a list of references, in some instances fairly minimal, but this is not always the case. This is a pity as one of the objectives of this series is to base "our knowledge of paediatric anaesthesia on scientific foundations" and without such data acquisition of knowledge in this specialty will continue to be based on upon words of experience and impressions. Whilst there is a considerable amount of important information presented in these lectures, they are often too superficial and brief to help the junior anaesthetist in the management of the condition being discussed. Perhaps these deficiencies were clarified during the discussion period following these lectures. This volume can be read with profit by all those involved with paediatric anaesthesia to stimulate further reading in these selected topics.

*Gordon H. Bush*

*An Introduction to Acupuncture: Treatment and Anesthesia*. By M. Salim. Published by Ajail Stores, Sukkur. Price Rs 50.

This book purports to be a comprehensive description of acupuncture techniques by an author who has written extensively on the subject.

It traces the development of acupuncture from ancient times and explains the theories of pulse variation, moxibustion, meridians, life forces, etc., that lie behind its practice. With the aid of numerous diagrams the author describes the acupuncture points on the body and how these may be used to cure all the ailments known to man.

The book does not confine itself solely to the practice of this mystical art and does incorporate a chapter on complications, which include haematoma, broken needles, etc., and does caution against ill-advised needle placement such as over the thorax or blood vessels. This, together with a chapter at the end of the book that deals with the more conventional western ideas of pain production and control suggests that the author believes that acupuncture and western medicines are not incompatible.

The construction, text and several of the descriptive terms are confusing, and some of the diseases mentioned, such as nocturnal pollution and unconsciousness caused by draught, are certainly unknown to the reviewers. For this reason it would perhaps be advisable to stick to some of the more home-grown books on the subject, such as those by Dr Julian Kenyon.

*K. Rogers*
*T. McCubbin*

## OTHER BOOKS RECEIVED

*Quantitative Acid–Base Physiology*. By Poul Kildeberg. Published by Odense University Press, Denmark. Pp. 206; illustrated; indexed. Price Dan. kr. 130.00.

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# Bulletin Européen de Physiopathologie Respiratoire

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* Articles written in French

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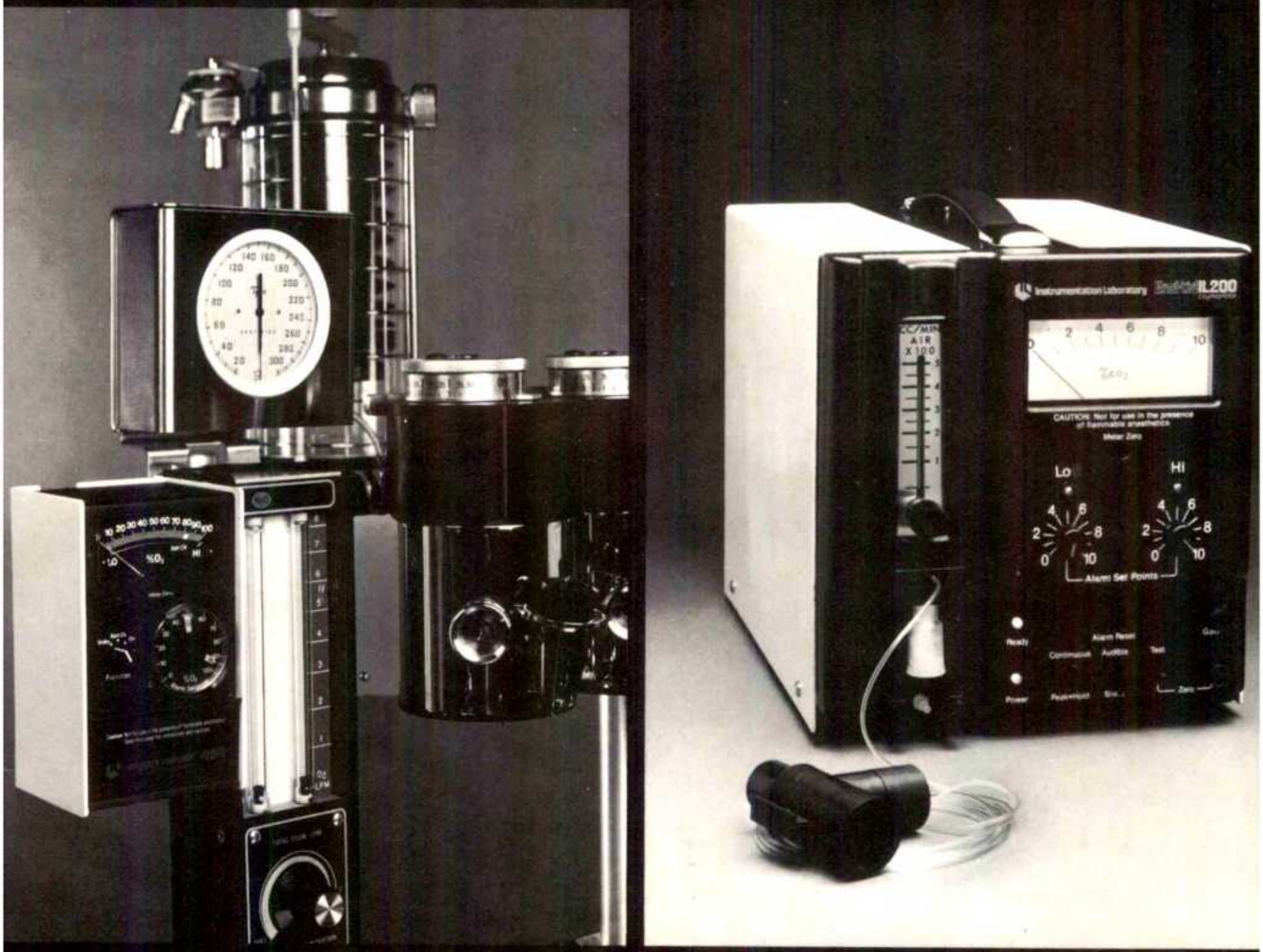

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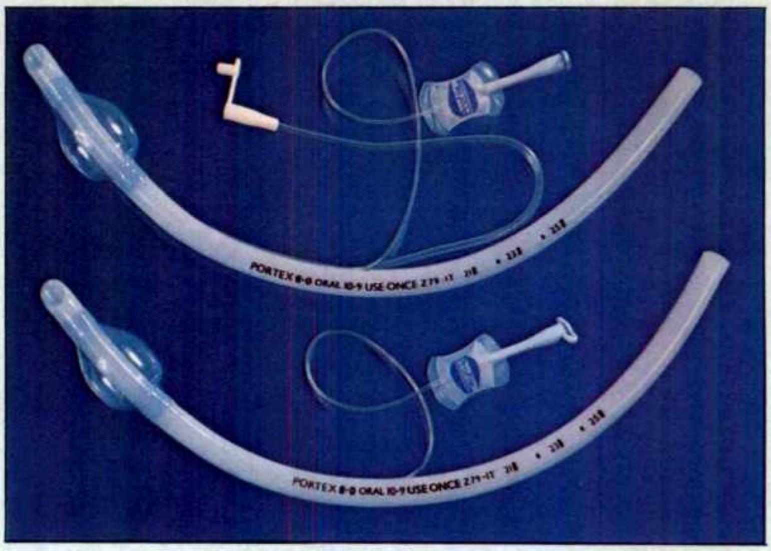

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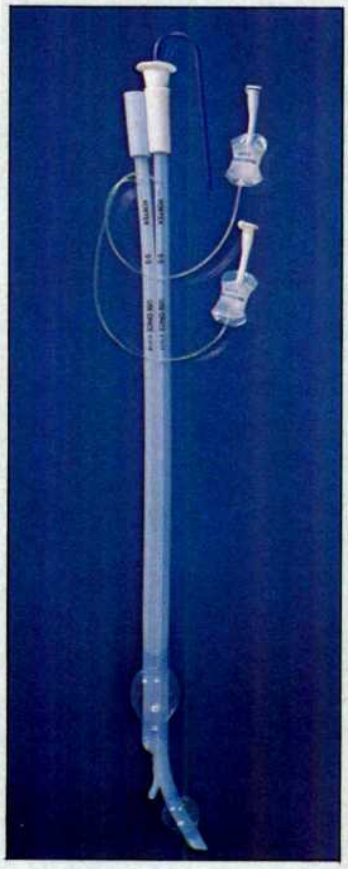

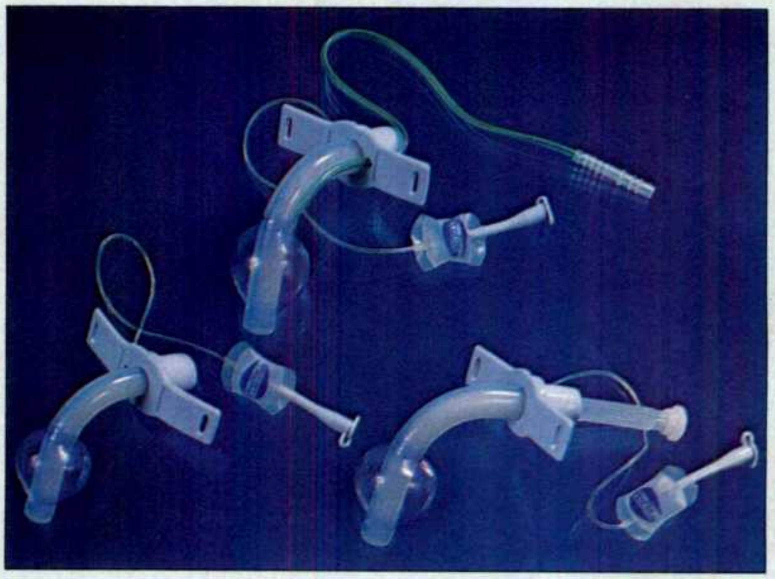

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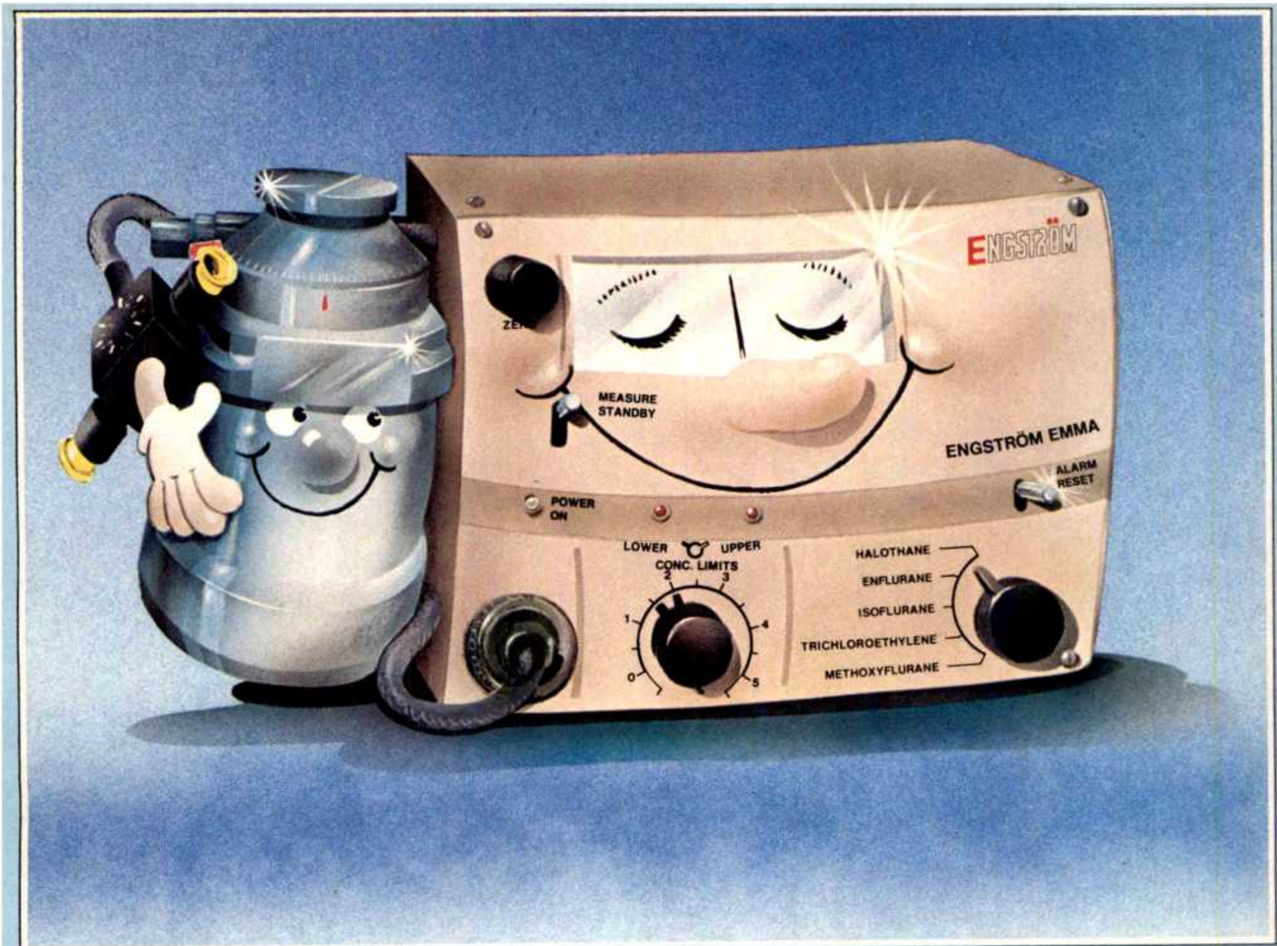

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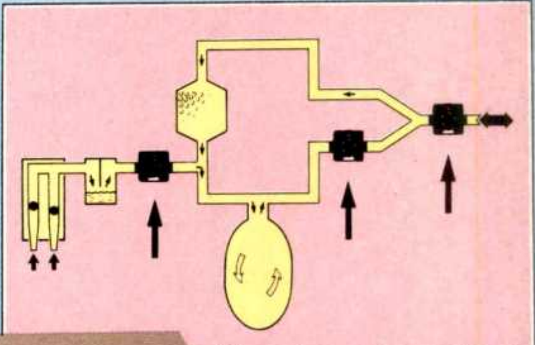

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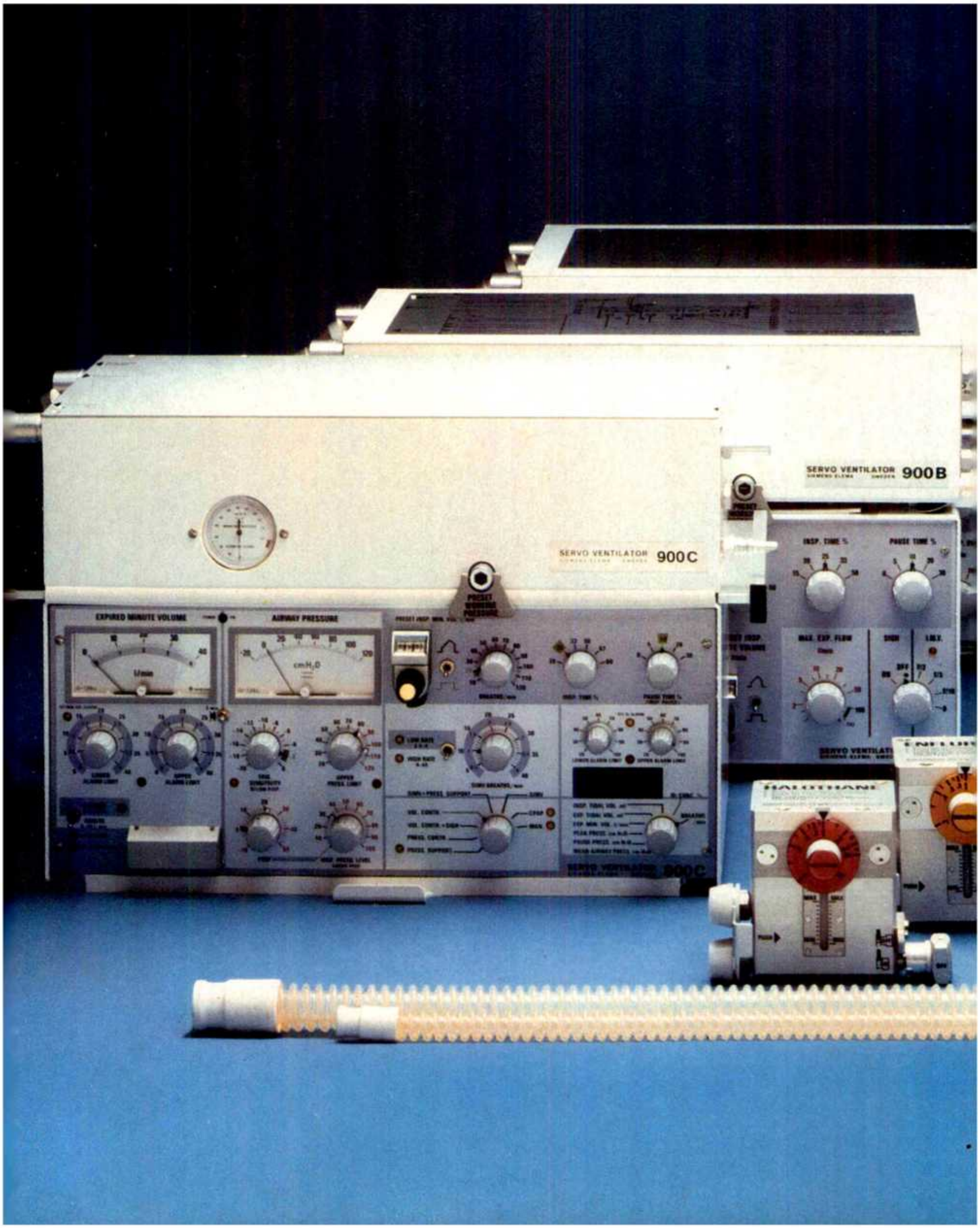
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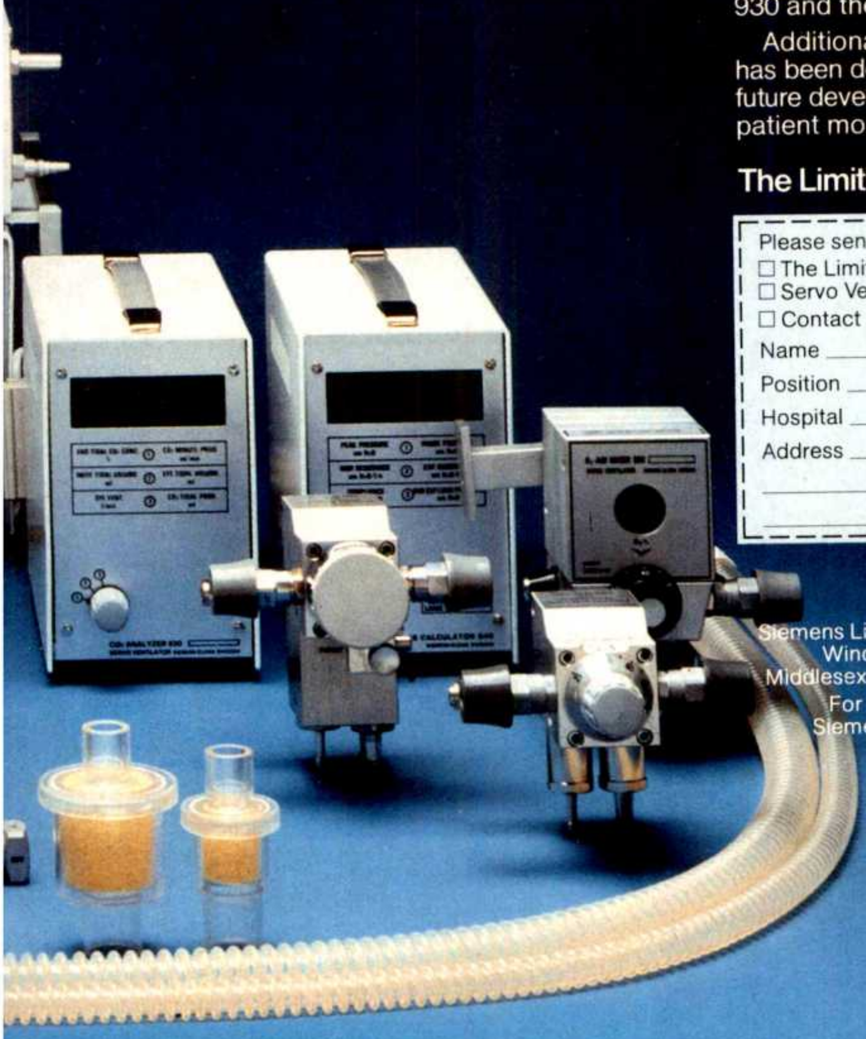

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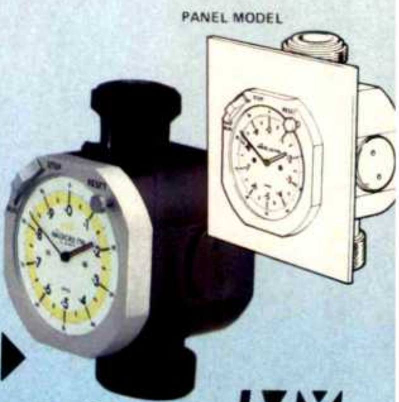

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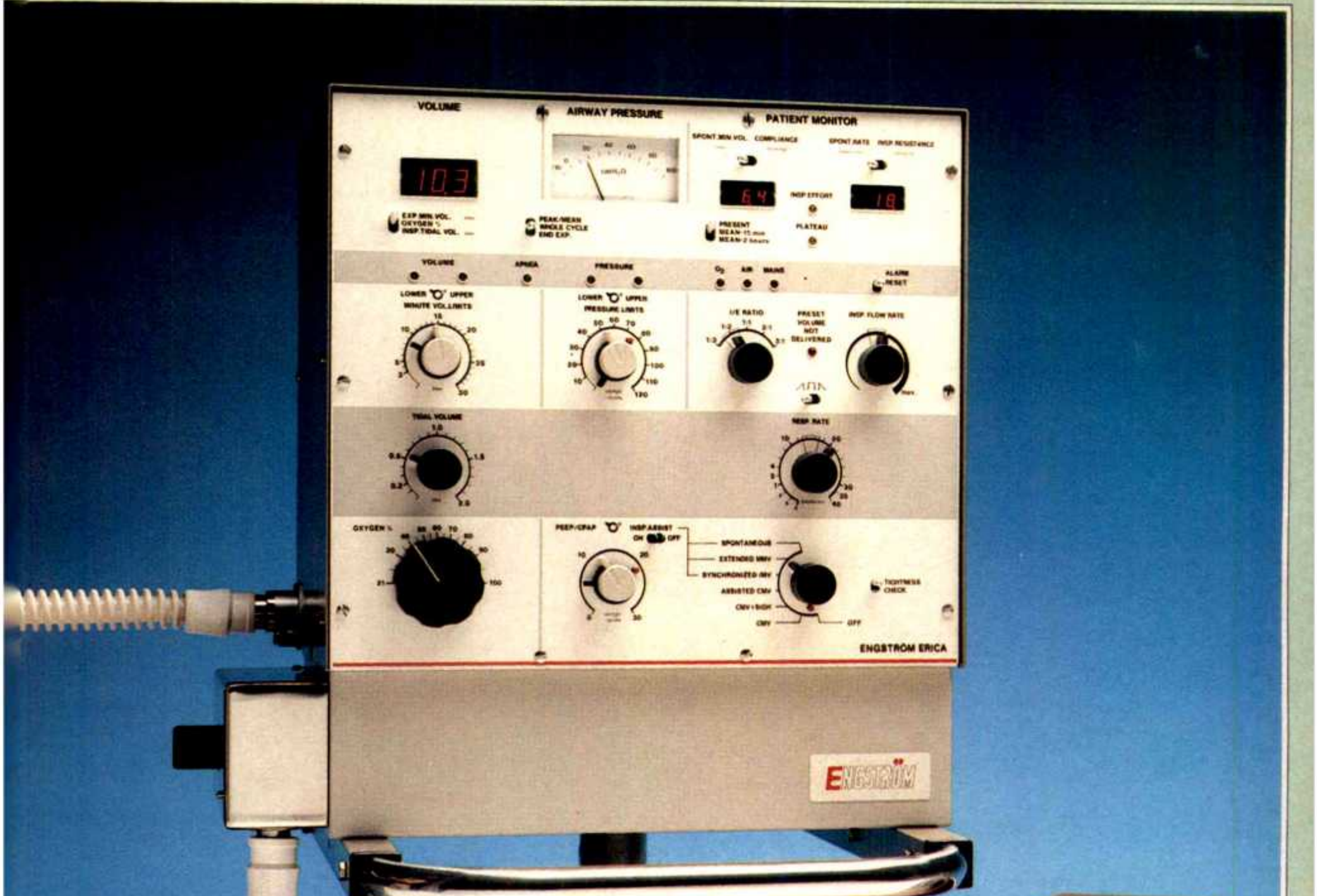

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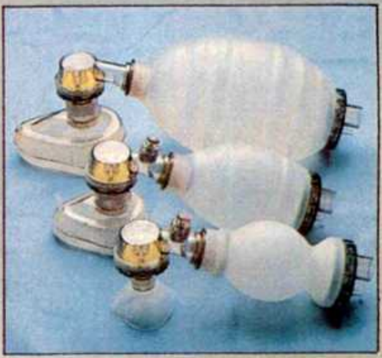

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chloride, ampoules of 1ml (0.3mg) or 2ml (0.6mg).
esic Sublingual tablet containing 0.2mg buprenorphine,
hydrochloride. **Uses:** As a strong analgesic for the relief
derate to severe pain. **Dosage and Administration:**
esic Injection: Adults: 1-2ml (0.3-0.6mg) by i.m or
v. injection, every six to eight hours or as required.
esic Sublingual: 1-2 tablets
.4mg buprenorphine)
ved under the
e, every 6 to 8
or as required.
ablet should not be
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esic is not at
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absolute contra-
ations for
esic. However,
should be taken
treating patients
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atory function
ngesic may
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respiration. Because buprenorphine has antagonist properties, it may precipitate mild withdrawal symptoms in narcotic addicts, and it should be given with care initially to patients previously treated with narcotic analgesics. Temgesic may cause some drowsiness; this could be potentiated by other centrally-acting agents, including alcohol. Ambulent patients should be warned not to drive or operate machinery if affected. Since buprenorphine is metabolised in the liver, the intensity and duration of its action may be affected in patients with impaired liver function. Until further information is available, Temgesic should be used with caution in patients receiving monoamine oxidase inhibitors, and it is not recommended for use during pregnancy. **Side Effects:** Drowsiness is the most common side effect. In common with other strong analgesics, nausea, vomiting, dizziness and sweating have been reported and may be more frequent in ambulant patients. Clinically significant respiratory depression has been observed rarely and only in the post-operative period. **Product Licence Numbers, NHS Price:** at January 1982. Temgesic injection 1ml— 44/0056. £5.52/pack 10 ampoules. Temgesic injection 2ml—44/0057. £9.89/pack 10 ampoules. Temgesic Sublingual PL44/0063. £6.00/pack 50 tablets. Irish Product Authorisation Nos. 1ml— PA27/3/1: 2ml —27/3/2. Temgesic Sublingual No. PA27/3/3. Additional information available on request from: Reckitt & Colman Pharmaceutical Division, Hull HU8 7DS.

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continuing relief from post-operative pain
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in 1ml

**Temgesic**
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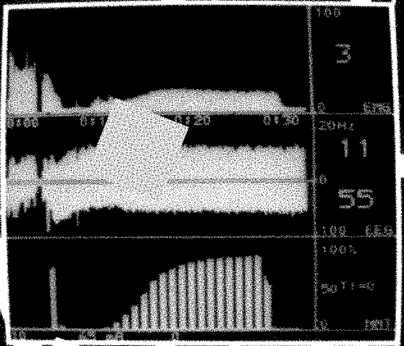

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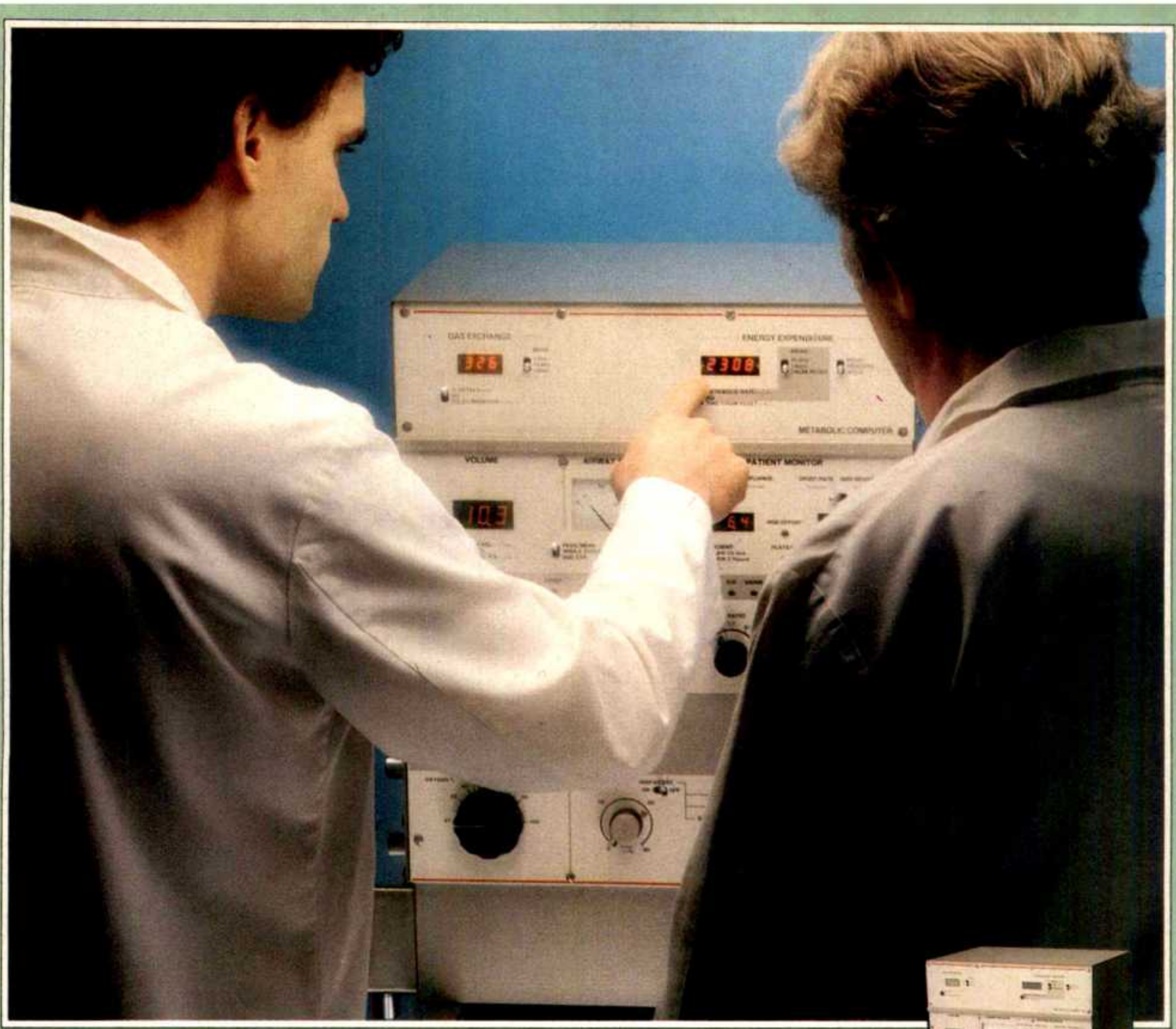

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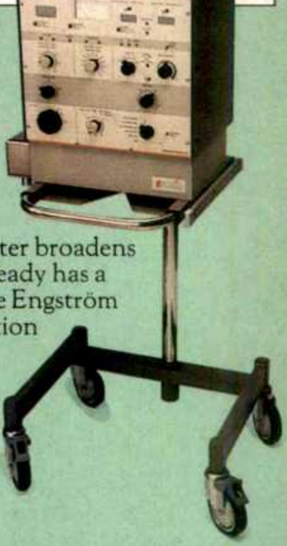

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When a drug is first mentioned it should be given the generic or official name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

### *Results*

Description of experimental results, while concise, should permit repetition of the experiments by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. Significance should be given as values of probability. The desired positions of tables and figures may be indicated by written instructions enclosed within lines and brackets, for example:

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(TABLE III near here)

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### *Discussion*

The discussion should not merely recapitulate the experimental results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

### *Acknowledgements*

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### *References*

There should be a table of references at the conclusion of the paper. These references should be arranged according to the Harvard system and in alphabetical order. In the text, the year of publication must follow the author's name, more than one paper in any year being indicated by a small letter (a, b, c,) after the date. In the references, the order should be author's name, followed by initials; year of publication in parentheses; title of paper to which reference is made; title of publication underlined with a single line (to indicate italics) and abbreviated in accordance with *Cumulative Index Medicus*; volume number in arabic numerals, underlined with a wavy line (to indicate bold face); the number of the first page in arabic numbers; thus Clarke, M., Evans, D. W., and Milstein, B. B. (1971). Long-term pacing with an inductive coupling system. *Br. Heart J.*, **33**, 65.

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The *British Journal of Anaesthesia* should be referred to as *Br. J. Anaesth.*

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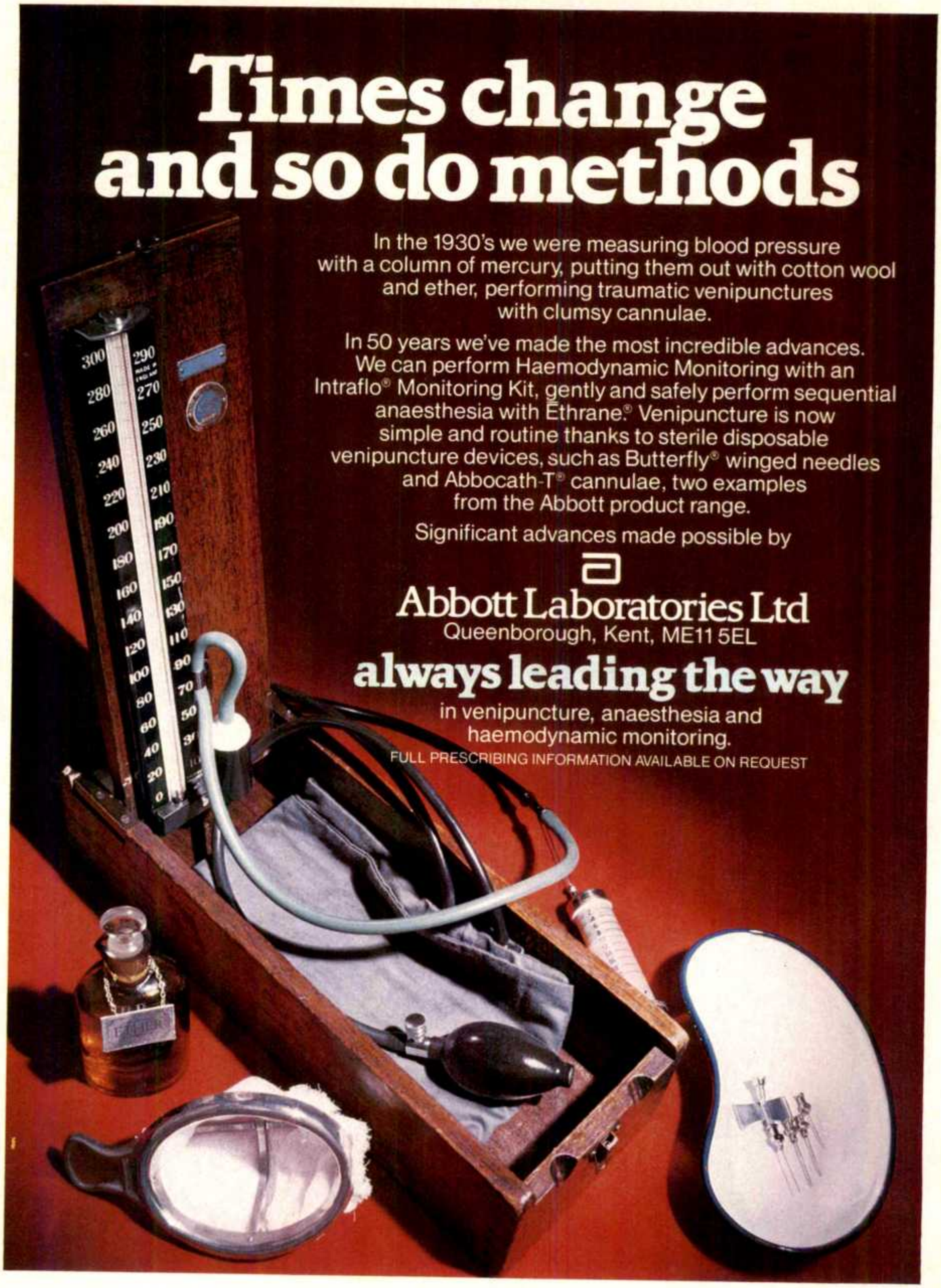

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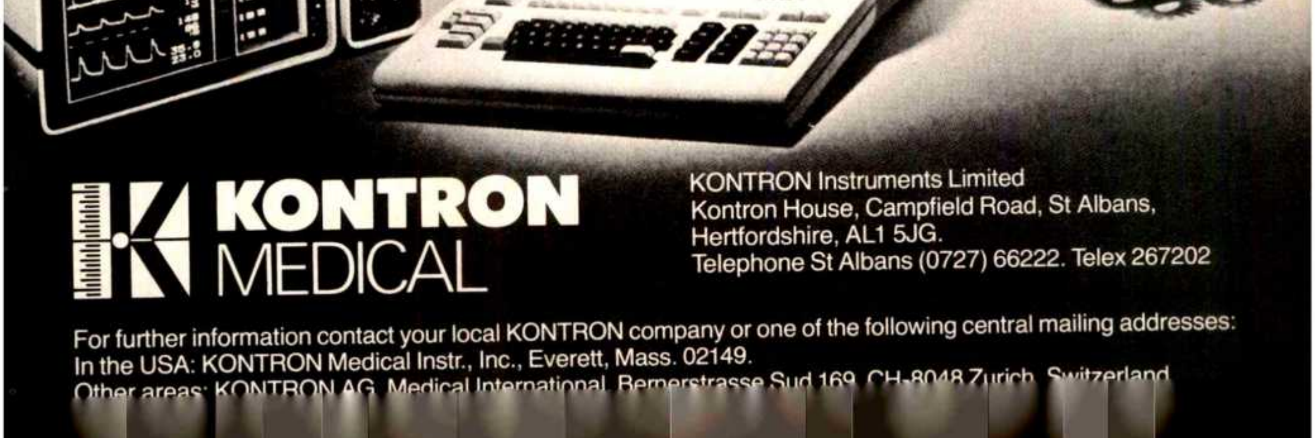

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It is proposed that a proportion of the Journal be devoted to correspondence each month. Every effort will be made to ensure that correspondence arising from papers in a recent issue is published without delay, and for this reason, relevant correspondence will be given priority over that pertaining to original research. Authors of correspondence concerning original work will receive proofs at the Editor's discretion.

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These should be corrected and returned to the sub-editor *within 48 hours of receipt.* Overseas contributors should return their proofs by airmail.

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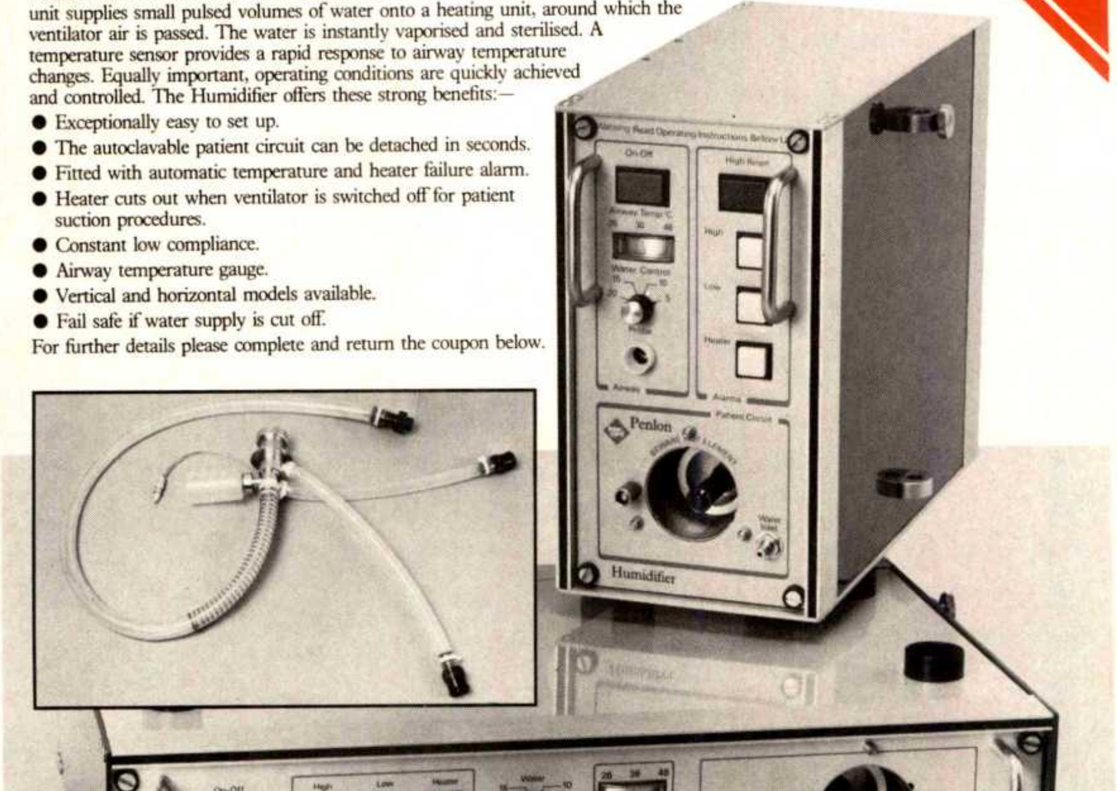

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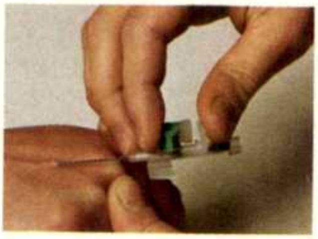

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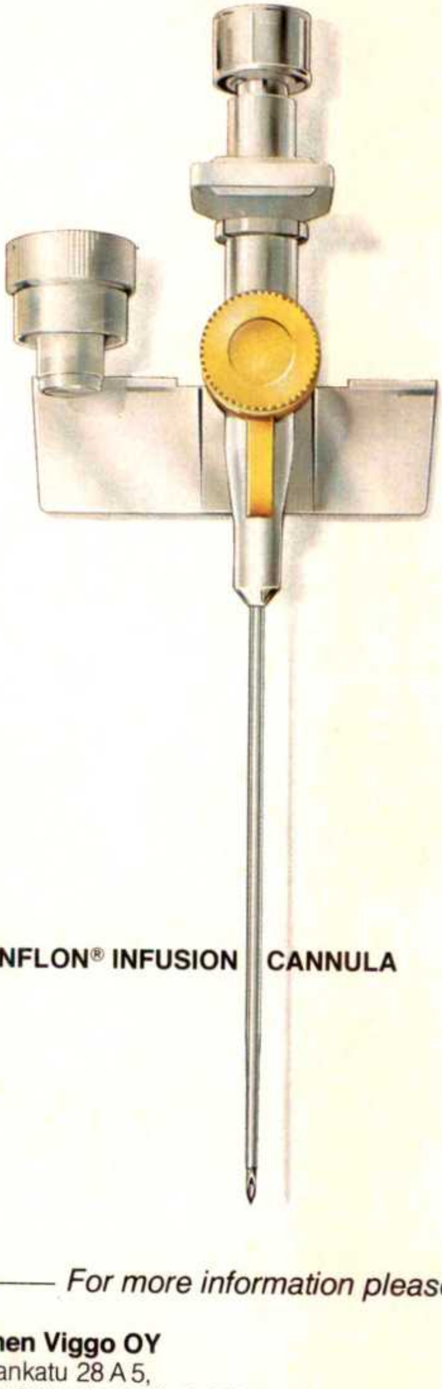

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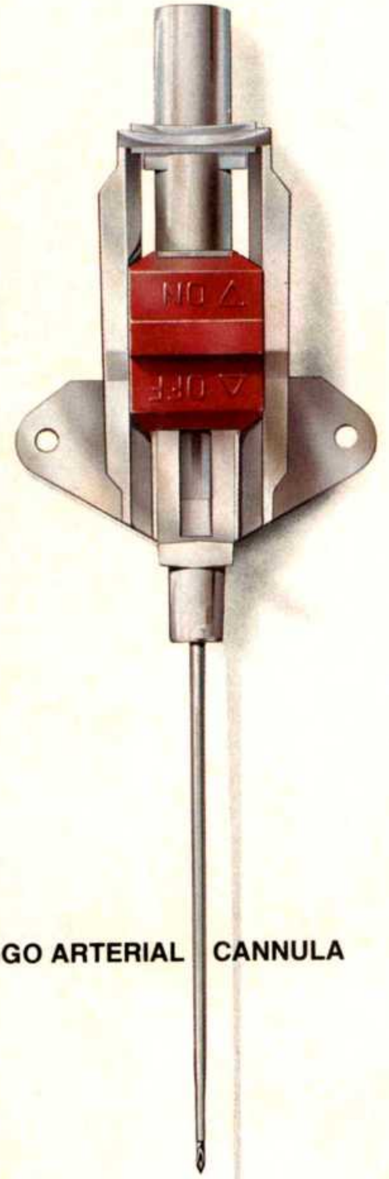

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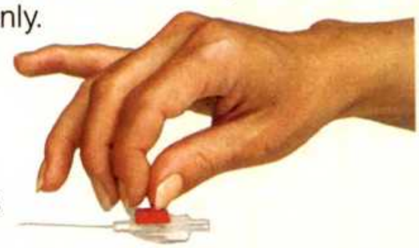

Here the FloSwitch is shown as an integral part of the Viggo Arterial Cannula, used primarily for pressure monitoring and serial blood gas sampling.

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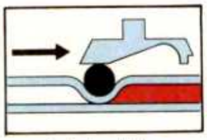

The principle of the FloSwitch is simple: When the switch is pushed forward a small metal ball is pressed down on the plastic tube in the FloSwitch hub hereby occluding the fluid path completely.

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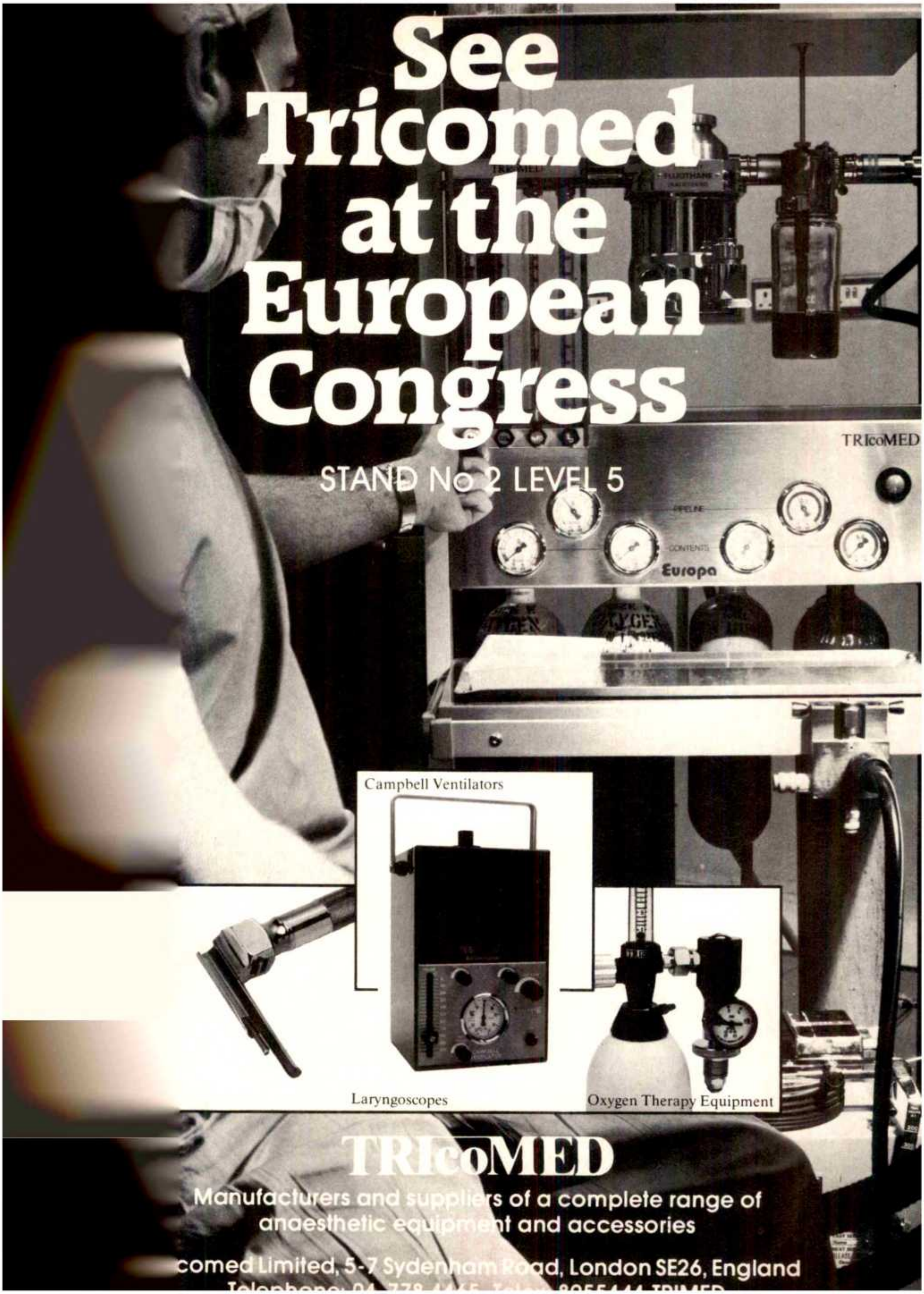

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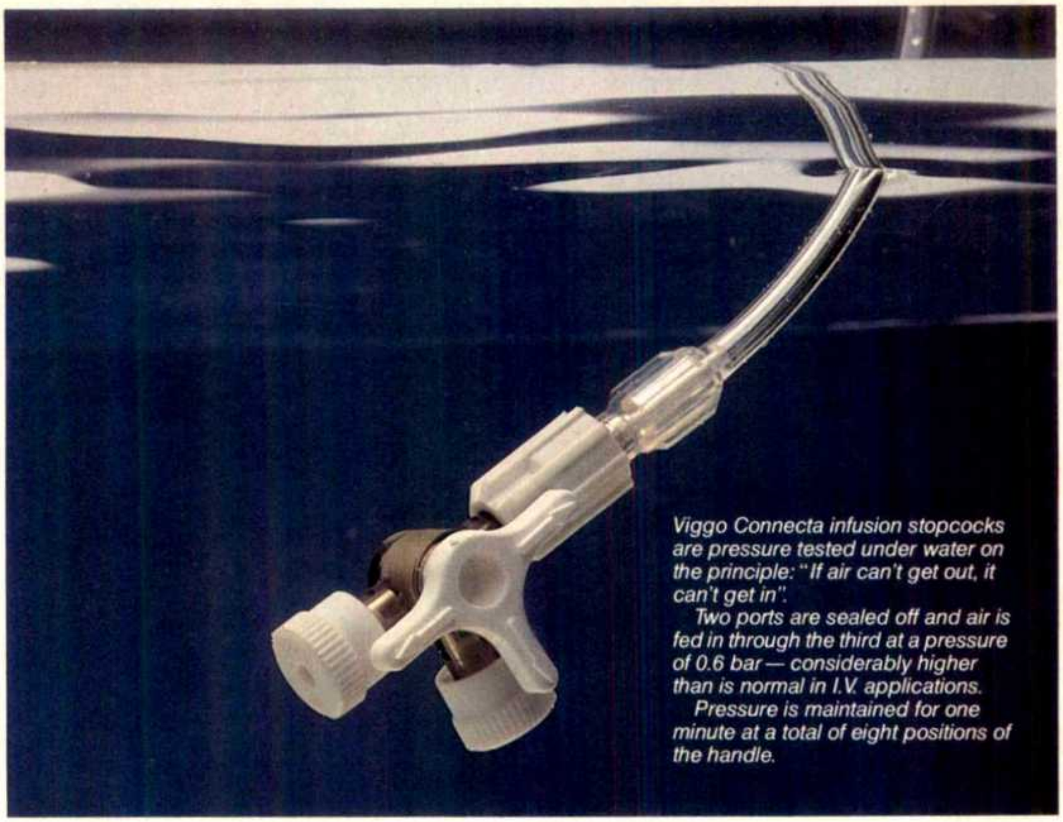

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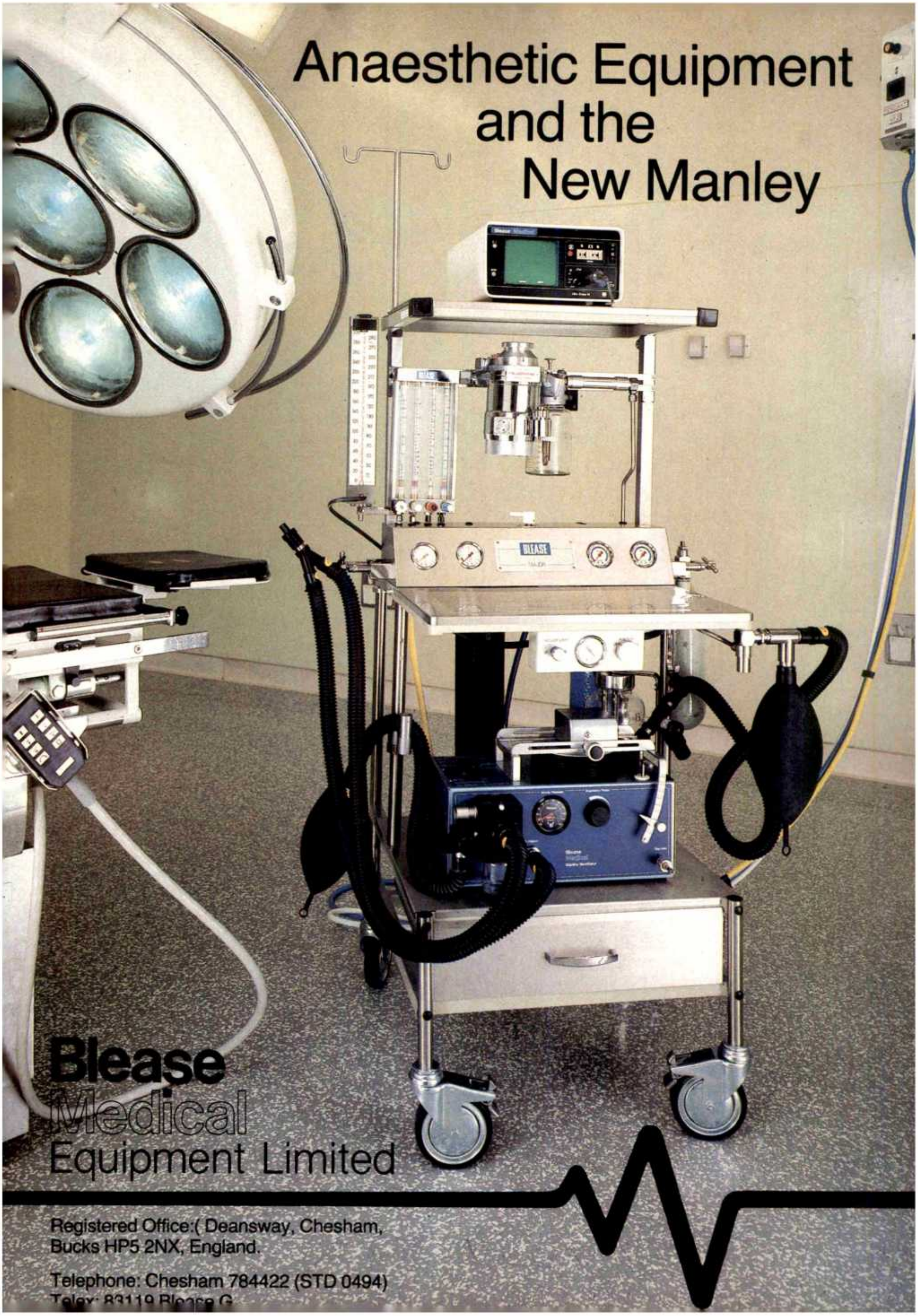

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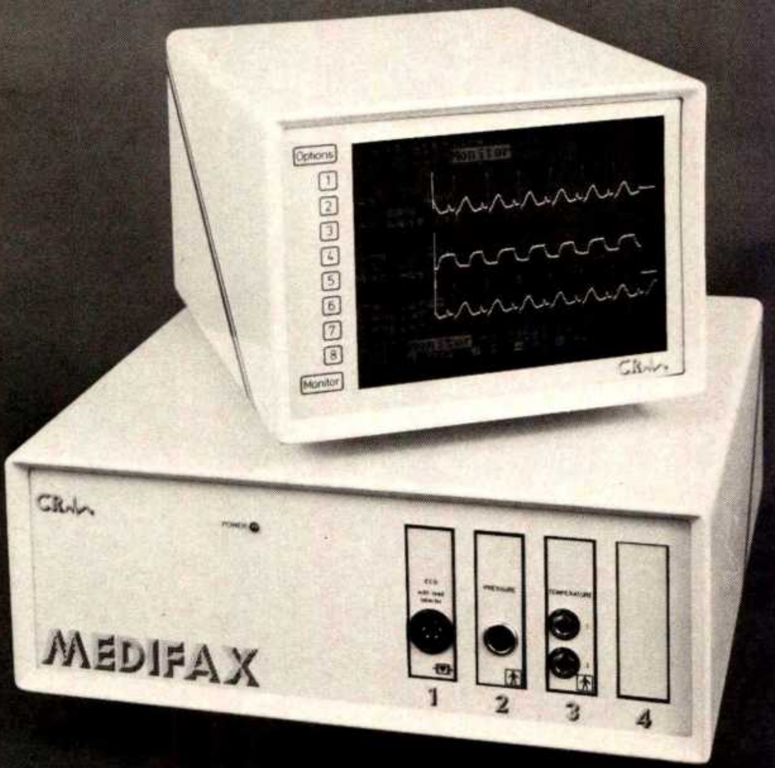

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# muscle relaxation-pure and simple

**Prescribing information**

**Indication** Muscle relaxation for surgical and anaesthetic procedures. **Dosage** Response is variable, but as a guide: Adults: 0.20-0.25mg/kg intravenously for approximately 20-30 minutes' relaxation, 0.30mg/kg for approximately 40 minutes' relaxation. These doses may be repeated as necessary. Children: 0.125 to 0.2mg/kg bodyweight. **Contra-indications** Hypersensitivity to alcuronium, myasthenia gravis; myasthenic (Eaton-Lambert) syndrome. **Precautions** Dosage requirements may be altered in renal impairment, hepatic and neuromuscular diseases, and by concomitant use of antibiotics of the polymixin and aminoglycoside groups, volatile anaesthetics, drugs with local anaesthetic properties, ganglion-blockers, electrolytes (Mg, Na, K, Ca). Avoid during pregnancy. **Side-effects** Hypotension and, less frequently, tachycardia. Some cases of anaphylactoid reaction have been recorded. **Presentation** Ampoules containing 10mg alcuronium chloride in 2ml packings of 10. **Basic NHS Cost** Alloferin ampoules 10mg x 10, £4.58 **Licence Number** 0031/5000 Alloferin is a trade mark.

### In both short and prolonged surgery

A single dose of Alloferin (0.20-0.25mg/kg) provides muscle relaxation for approximately 20-30 minutes[2] and a 0.30mg/kg dose gives about 40 minutes of relaxation. The relaxation can be maintained for longer procedures with "no noticeable accumulation" of Alloferin,[3] and the number of repeat doses required is similar to that with tubocurarine or pancuronium.[4]

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Alloferin allows blood pressure and heart rate to be kept within acceptable limits in most patients due to lack of marked histamine-releasing, ganglion-blocking or vagolytic actions.[2,5,6]

### Easy reversal for uncomplicated recovery

Alloferin has been found to be easier to reverse with neostigmine than either pancuronium or tubocurarine.[4]

---

**References** 1. Brit.J.hosp.Med.,1980,*23*,153 2. Ann.Chir.Gynaec.,1977,*66*,113 3. Europ.J.clin.Pharmacol.,1980,*17*,449 4. Anesth.Analg.curr.Res.,1971,*50*,926 5. Int.Anesth.Clins,1979,*17*,13 6. Brit.J.Pharmacol.,1980,*70*,501

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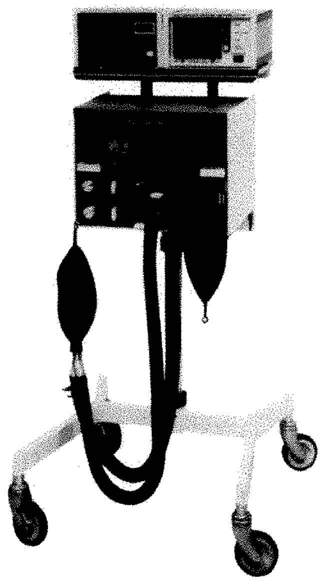

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**Indications**
Intravenous sedative cover before and during unpleasant surgical and medical procedures.
Status epilepticus; convulsions due to poisoning; acute muscle spasm; acute anxiety or agitation; delirium tremens; tetanus.

**Dosage**
**Adults:**
Usually 10 to 20mg (approximately 0.2mg/kg body-weight) but more may be necessary on occasions. Dosage may be repeated as necessary.
**Elderly patients:**
Half the usual adult dose.

**Precautions and side-effects**
Avoid alcohol; avoid driving or operating machinery.
In patients with organic cerebral changes or cardiorespiratory insufficiency IV injections of Valium Roche should not be employed unless in an emergency or in hospital. If indicated it should be given slowly and in reduced dosage.
The possibility of intensified sedative effects and severe respiratory and cardiovascular depression should be considered if central depressant drugs are given in conjunction.
Should not be used in early pregnancy unless absolutely indicated.
Intravenous injection may be associated with local reactions including thrombophlebitis.

**Presentation**
Ampoules containing 10mg diazepam in 2ml and 20mg in 4ml, in packings of 10.

**Product Licence Numbers**
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**Basic NHS Cost**
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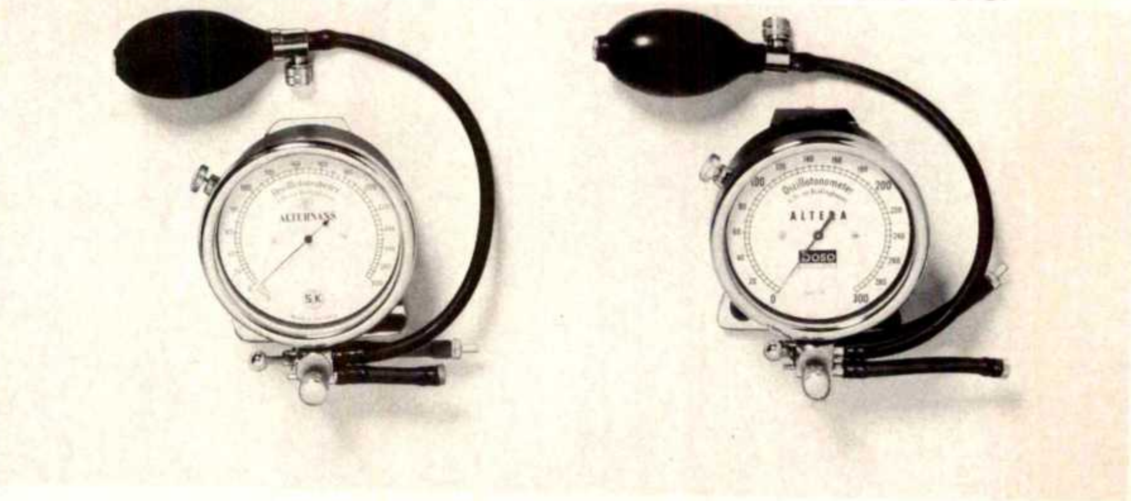


# Ativan*

lorazepam

## ensures a 'stress-free' patient

**dependable anxiolytic effect without over-sedation**[1,2,3]

**minimal effect on respiration and other vital functions**[2,6,7]

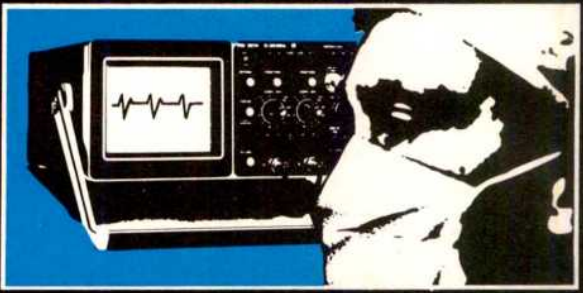
**predictable lack of recall of unpleasant events**[1,6]

**allows nursing staff to give oral premedication to the entire list simultaneously**[4,5]

**potent anti-convulsant effect provides more sustained seizure control than diazepam**[8]

## In premedication

Patients premedicated with Ativan are calm and relaxed but not deeply sedated, so they remain co-operative. Use of Ativan tablets avoids the need for injections, and they can be given to all the patients on the list at one time, providing anxiolytic cover even if adjustments to the list have to be made. Lack of respiratory depression and other unwanted cardiovascular effects provides an added margin of safety for even the poor risk patient and lack of recall for unpleasant events ensures excellent patient acceptance.



## In the intensive therapy unit

Parenteral Ativan effectively relieves anxiety without over-sedation or compromising pulmonary or cardiac function. Dosage may be titrated to produce a patient who is calm but may be roused for monitoring or assessment of level of consciousness. Prolonged administration provides an even level of anxiolysis and sedation with minimal cumulative effects and no difficulty in weaning patients off the ventilator. Relative lack of pain, tissue damage and thrombophlebitis at the injection site compared with diazepam and lack of recall of experience ensures Ativan is particularly well accepted by I.T.U. patients.

**References:** 1. Johnstone M. (1976) *Anaesth.*, **3**, 868-872. 2. Dundee J. W. *et al.* (1977) *Br. J. Anaesth.*, **49**, 1047-1055. 3. Paymaster N. J. (1973) *Curr. Res. Med. Opin.* **1** (5) 317-322. 4. Turner D. J. (1973) *Curr. Res. Med. Opin.*, **1** (5) 302-307. 5. Studd C. and Eltringham R. J. (1980) *Anaesth.* **35**, 60-64. 6. Cormack R. S. *et al.* (1977) *Br. J. Anaesth.*, **49**, 351-360. 7. Dodson M. E. *et al.* (1976) *Br. J. Anaesth.*, **48**, 611-612. 8. Walker J. E. *et al.* (1979) *Ann. Neurol.* **6**, (3) 207-213.

**Prescribing Information. Presentation** Ativan tablets are blue, oblong in shape, containing 1mg lorazepam and yellow, oblong containing 2.5mg lorazepam. Ativan injection is a clear, colourless solution containing 4mg/ml lorazepam, supplied in 1ml quantities in clear glass ampoules. **Uses** Ativan is indicated for mild, moderate or severe anxiety, phobic or obsessional states. Anxiety in psychosomatic, organic or psychotic illness. Premedication before operative dentistry or general surgery. The injection is also indicated in the control of acute anxiety states and status epilepticus. **Dosage and Administration Tablets** Anxiety states—up to 10mg/day in divided doses. Premedication—2-3mg the night before operation 2-4mg one or two hours before surgery. Ativan tablets are not recommended for young children. **Injection** May be given i.v. or i.m. Care should be taken to avoid injection into small veins and intra-arterial injection. *Preparation of the injection*—Ativan injection is slightly viscid when cool. To facilitate injection it may be diluted 1:1 with normal Saline or Water for injections B.P. immediately before administration. If given i.m. it should always be diluted. Ativan injection is presented as a 1ml solution in a 2ml ampoule to facilitate dilution. The injection should be given slowly except in the control of status epilepticus when rapid injection is required. Ativan should not be mixed with other drugs in the same syringe. Premedication 0.05mg/kg (3.5mg for average 70kg man) i.v. 30-45 minutes before surgery (for maximum lack of recall effect) i.m. 1-1½ hours before surgery. I.T.U. 0.025-0.05mg/kg 4-6 hourly (dependant on the desired degree of anxiolysis/sedation). Anxiety 0.025-0.03mg/kg (1.75-2.1mg for average 70kg man). Status epilepticus: Adults: 4mg i.v. Children: 2mg i.v. Except in the control of status epilepticus Ativan injection is not recommended for children. **Contra-indications** Patients with a previous history of sensitivity to benzodiazepines. Ativan injection is not recommended for out-patient use unless the patient is accompanied. **Precautions and Warnings** Concomitant administration with centrally-acting CNS depressant drugs including alcohol, will potentiate their depressant effects. Should be used with care in patients with severe impairment of renal, hepatic function. Elderly patients may require reduced dosage. Should not be administered during pregnancy unless in the judgement of the physician such administration is clinically justifiable with special care in first trimester. Patients should be cautioned against driving or operating machinery until it is established that they do not become dizzy or drowsy whilst taking Ativan tablets. Following the injection patients should not drive or operate machinery within 24 hours and should be advised not to take alcohol. Prolonged or excessive use of benzodiazepines may occasionally result in the development of some psychological dependence with withdrawal symptoms on sudden discontinuation. Treatment in these cases should be withdrawn gradually. Following use of the injection, patients should remain under observation for at least 8 hours and preferably overnight. **Side-effects** Daytime drowsiness may be seen initially and is to be anticipated in the effective treatment of anxiety, imbalance or ataxia is an indication of excessive dosage. Occasional confusion, hangover, headache on waking, dizziness, blurred vision and nausea have been reported. **Pharmaceutical precautions** Tablets—store in a cool, dry place. Injection—store between 0°-4°C and protect from light. **Legal Category** POM. **Package Quantities** 1mg and 2.5mg tablets are supplied in boxes of 100. The injection is supplied in 10 x 1ml ampoules per pack. **Hospital price**—as per local contract.
**Product licence Numbers** 1mg tablet 0011/0034; 2.5mg tablet 0011/0036; injection 0011/0051. Further information is available on request.
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) Leon A, Jr. – Journal of the National Society
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) Wong, M. et al – Catheterization and
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**Prescribing information**

1. Moore DC 1979 "Regional Anesthesia Techniques" VI P34.

**Presentations, Product Licence numbers and Basic NHS cost** (exclusive of VAT).

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See data sheet for recommendations for other blocks.

**Contra-indications, warnings, etc.** *Precautions:* As with all local analgesic solutions, every care should be taken to avoid accidental intravascular injection and to ensure that the cuff does not leak in intravenous regional analgesia. **Side effects.** Hypotension after extradural or autonomic block may occur commensurate with such procedures.
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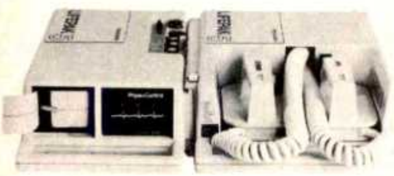

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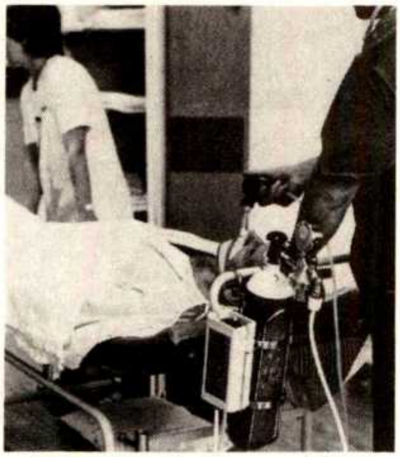

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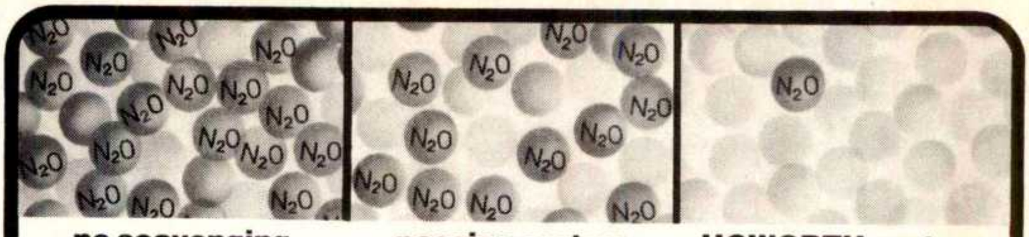

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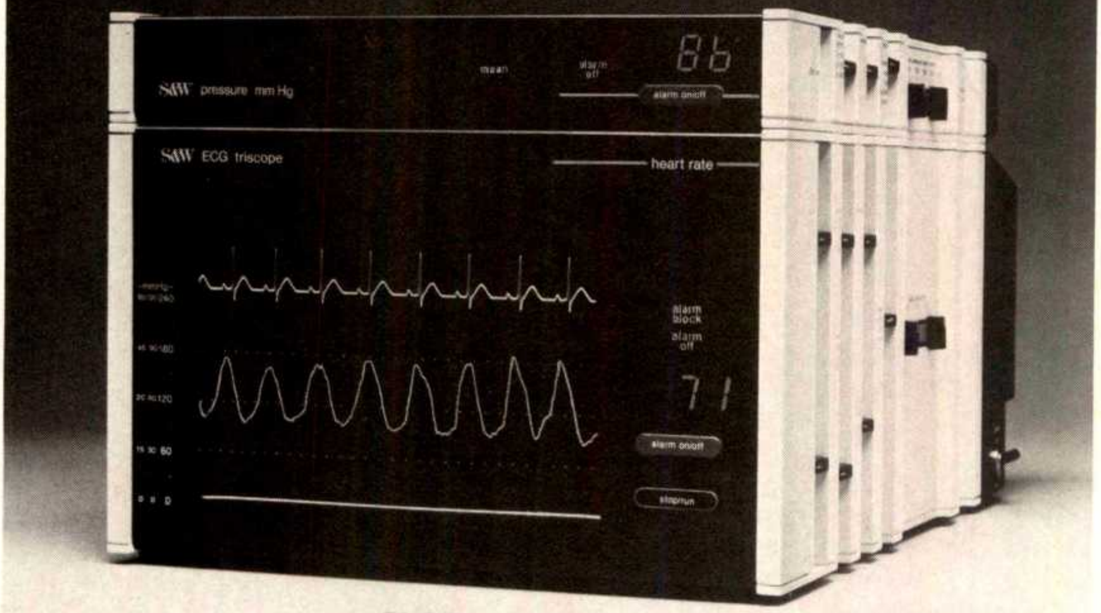

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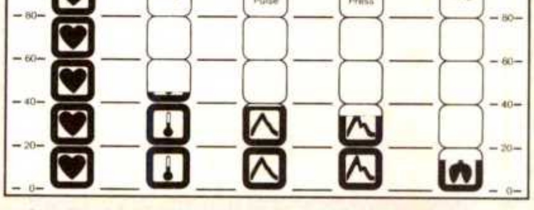

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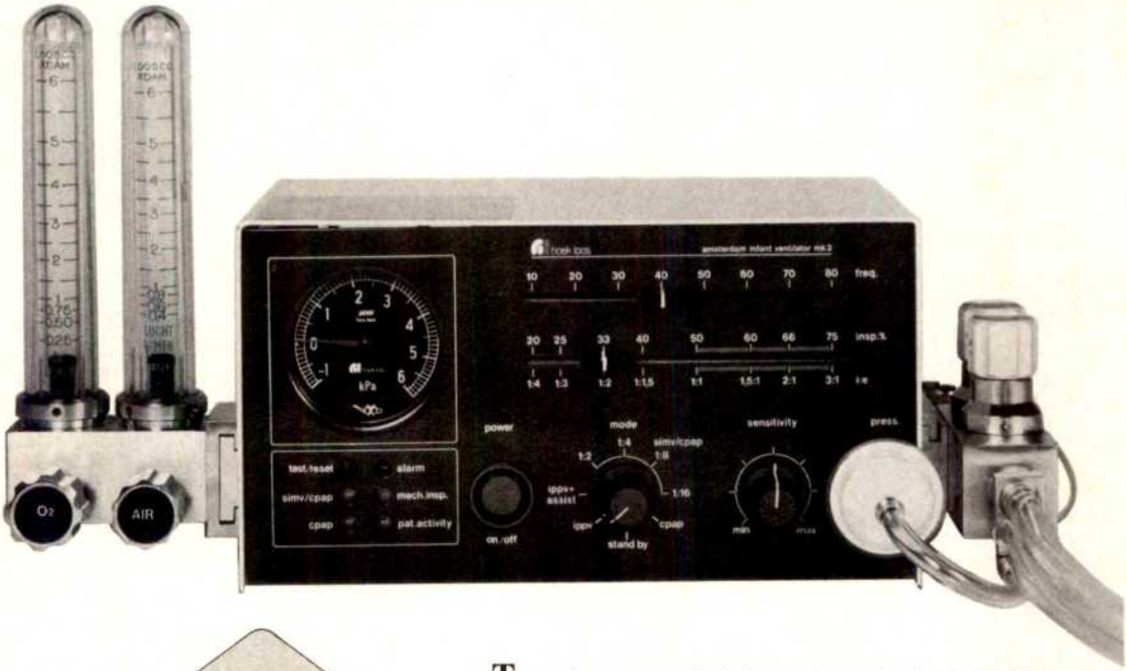

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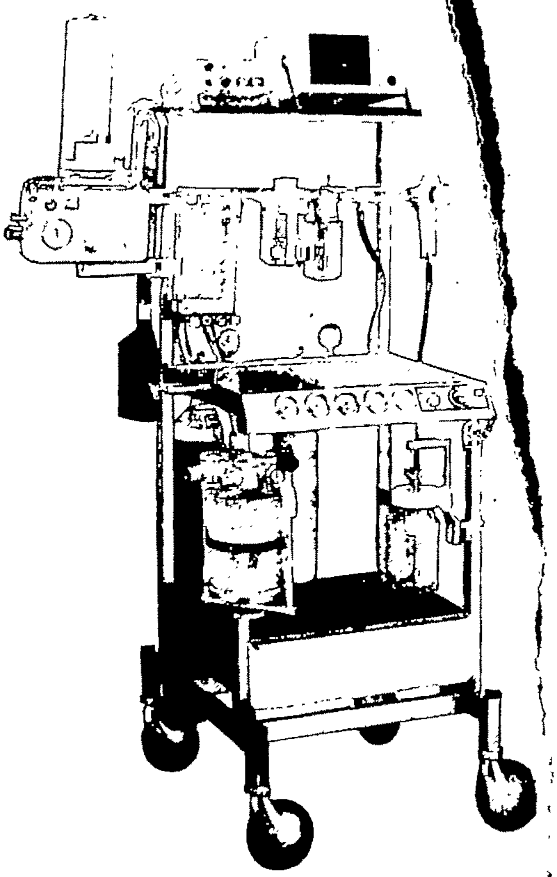

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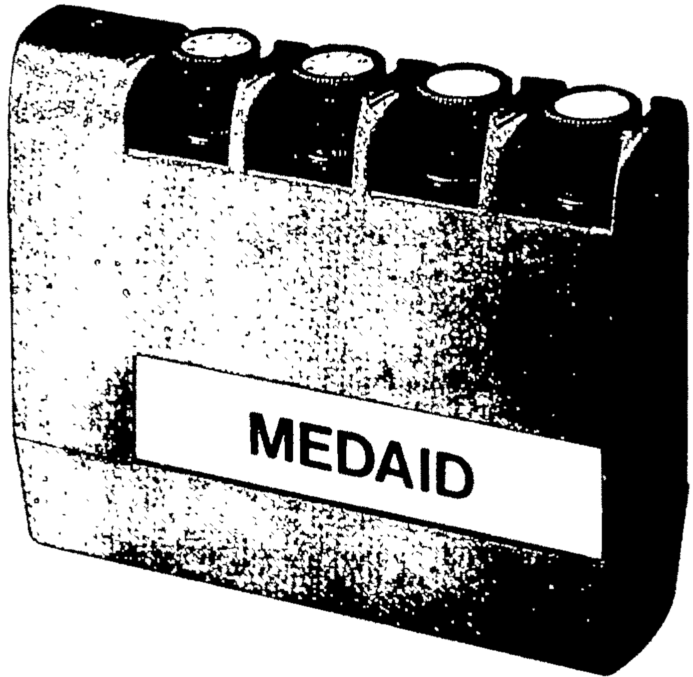

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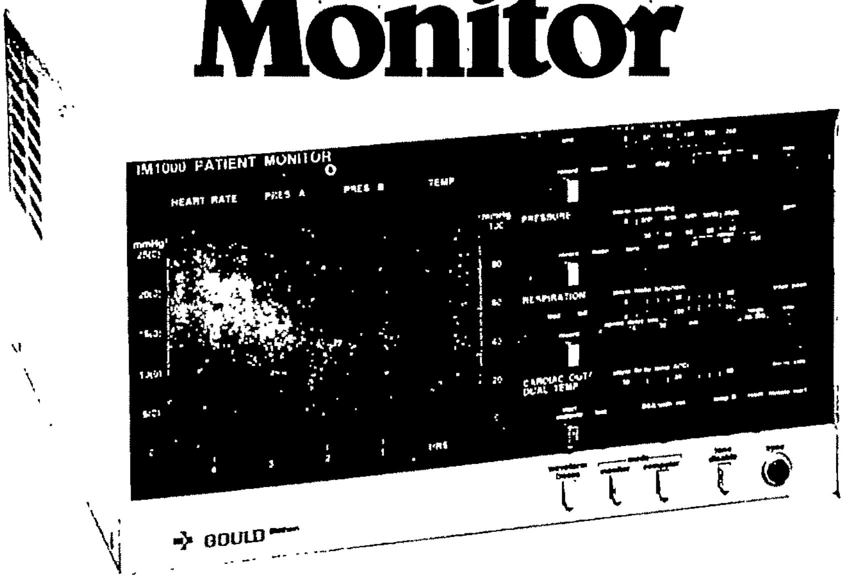

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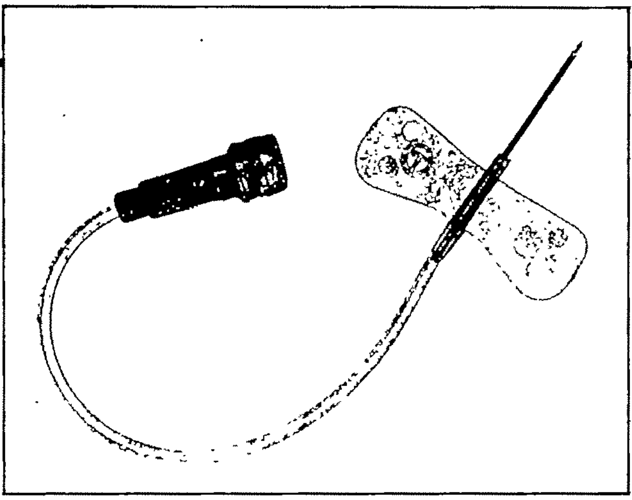

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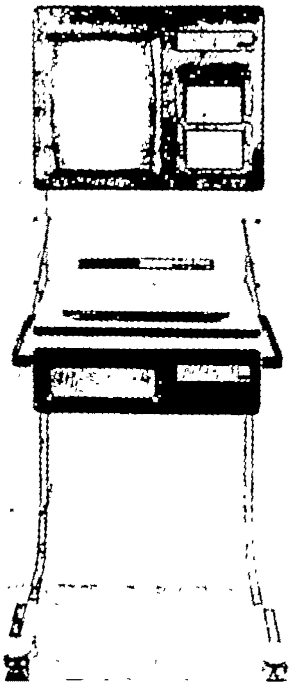

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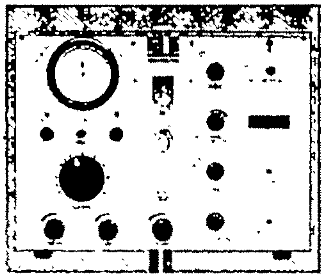

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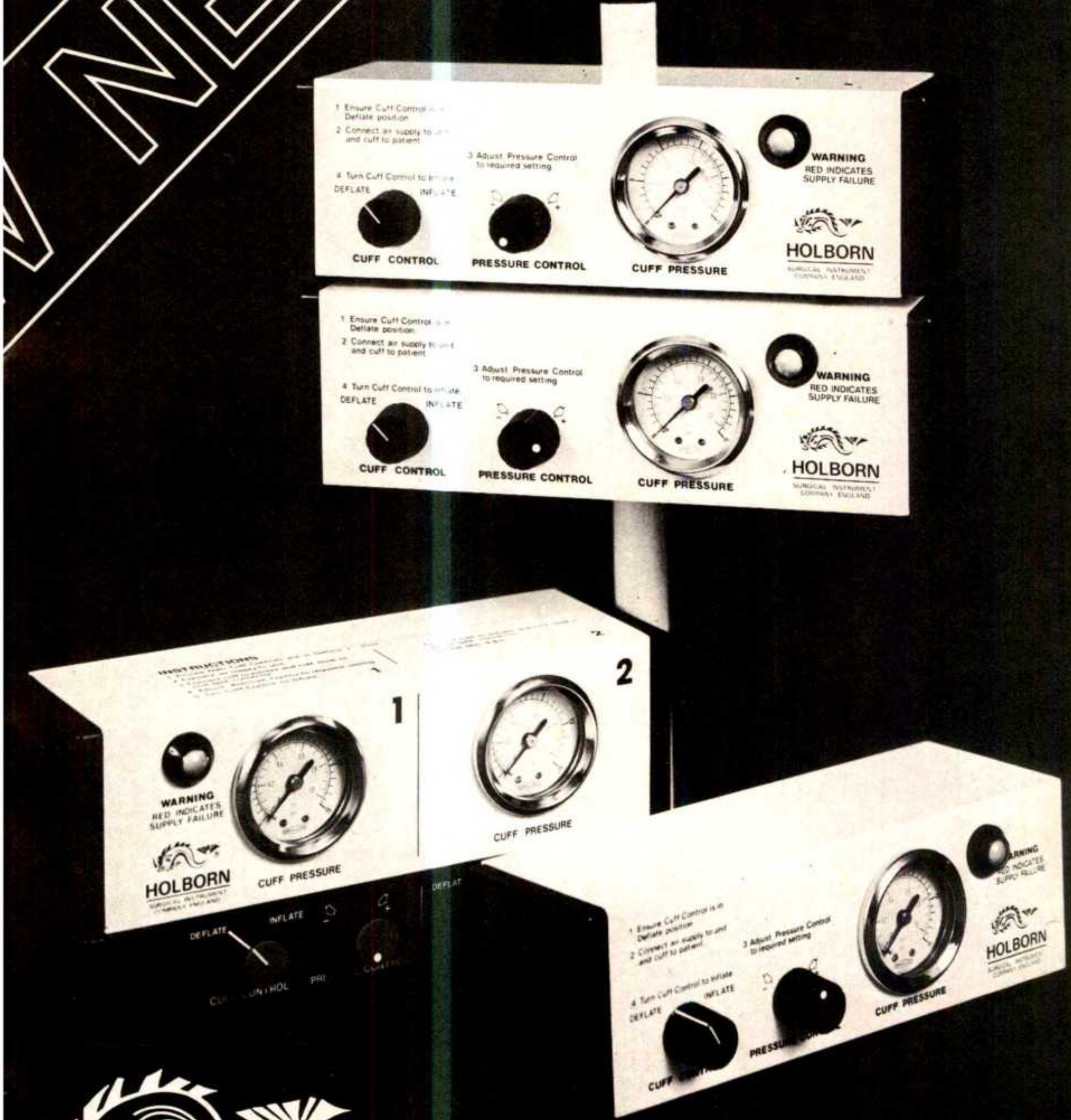
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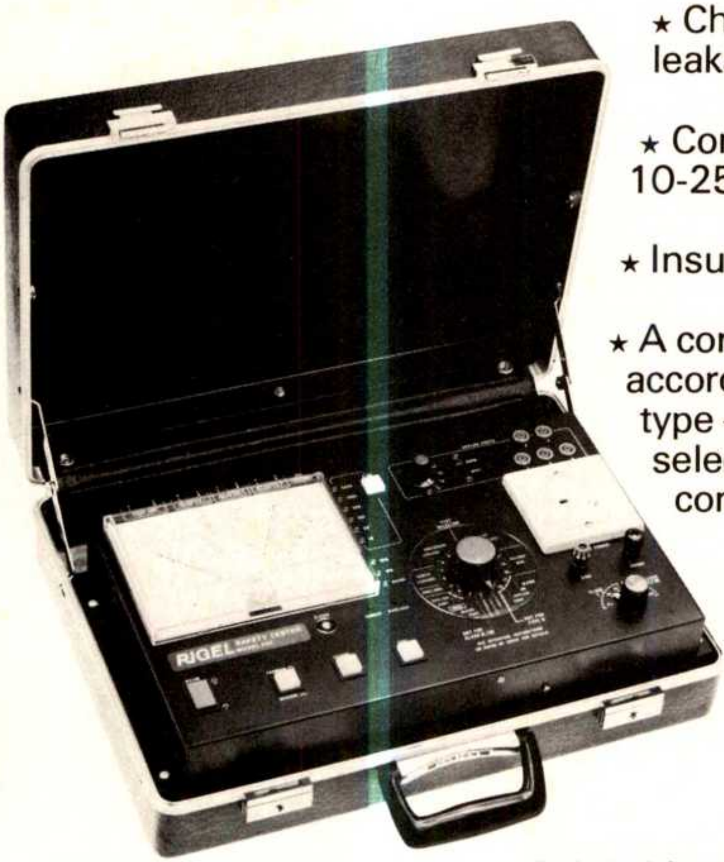

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 54, No. 8 AUGUST 1982

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# EDITORIAL

## VIth EUROPEAN CONGRESS OF ANAESTHESIOLOGY

The publication of this issue gives us an opportunity to welcome our colleagues particularly from Europe but also from many other parts of the world, to the VIth European Congress of Anaesthesiology in London. Their hosts in British anaesthesia have arranged a social and scientific programme which they hope will be worthy of the participation of their guests.

The frequency of large international congresses dictates that each of our countries will have a chance to act as host only once in a lifetime. It is particularly pleasing, therefore, that the VIth European Congress has come to London in the year of the Golden Jubilee of the Association of Anaesthetists of Great Britain and Ireland. When *British Journal of Anaesthesia* was founded, in 1923, the first editorial called for an organization to represent anaesthetists in these islands. At that time there were only two organizations in Britain which were dedicated exclusively to the interests of anaesthesia, the section of anaesthetics of the Royal Society of Medicine in London and the Scottish Society of Anaesthetists. Both were, and happily still are, active groups; perusal of the early pages of this Journal suggests that, although many miles apart at the time of relatively poor opportunities for travel, they appeared to be engaged in a dialogue with each other on the relative merits of chloroform and ether as the anaesthetic of choice! More than half a century later the affairs of anaesthesia in Britain and Ireland have become more sophisticated and more complex (if not always more interesting) and the Association of Anaesthetists fulfills the leading political role in the specialty in these countries. We offer to the President and Council our warm congratulations on this anniversary.

For some of the more senior members of our specialty this will be the second occasion in which London has been the venue for an international meeting. In 1968 the World Congress was held here, an event attended with great success. In almost every country in the world the fourteen years since that World Congress have been years of great change. In the continent of Europe there has been particularly impressive progress in the academic base of anaesthesia. It is especially satisfying for this Journal to have been in receipt of an increasing number of clinical and scientific reports of good quality from research groups throughout Europe whose standards are equal to those anywhere in the world. It is our confident hope that the scientific programme of the present Congress will reflect this.

Within the United Kingdom itself the interval since the last international congress has been a time of equally important change. The early 1970s was a period in which there was phenomenal growth of academic departments of anaesthesia throughout the country, and to many it seemed that there would be almost a guarantee of continued growth of this type in the future. Britain, like other countries, has become the victim of international recession with added national influences as a consequence of a virtual revolution in economic thinking on the part of government. Curtailment of public expenditure has hit universities in a particularly savage manner and every academic department of anaesthesia has been affected. In most cases there has had to be a radical curtailment of plans, and in a few a battle to survive at all. Although the health services have been less affected than the universities, there is ample evidence that the expansionist era is over. There is widespread acceptance of the fact that the National Health Service is not able to offer an open-ended commitment to the population in all matters of health care and that the private sector of our health services should receive more encouragement than has been the case in the past. This may have important implications for postgraduate training and development in medicine generally and anaesthesia in particular. There is little doubt that the introduction of the National Health Service in Britain, in 1948, was an important factor in allowing the relatively early development of anaesthesia in this country and any modification of the patterns of health care delivery must be monitored carefully lest the progress and achievements of the past be lost.

Although these are worrying times it would be wrong to give the impression to our visitors that our country and our specialty are in decline. Changing circumstances force on us reanalysis of objectives and priorities, but they are not automatically grounds for pessimism. Anaesthetists in Britain greatly look forward to welcoming our visitors. All who come can be assured of a warm welcome and an opportunity to reaffirm old friendships and to make new ones.

*Alastair Spence*

# EDITORIAL

## ROTTERDAM MEETING ON THE HISTORY OF ANAESTHESIA

Henry Ford of Ford Motors is credited with the aphorism that history is bunk and A. J. P. Taylor with the suggestion that the only lesson to be learned from history is that the fact that men never learn the lessons of history. Nonetheless it is, to say the least of it, interesting to learn the facts concerning the introduction of new anaesthetic drugs and those who were responsible for them, and especially to meditate on the times when such advances were made and what was the ethos thereof.

The history of anaesthesia really falls into two sections. First there is the ether and chloroform era which began with Morton's administration of ether in Boston, in 1846, and extended until about the beginning of the 1939–45 War. About this time, however, there was a revolution in the practice of anaesthesia and a large number of those who were involved are still alive, but in the nature of things cannot expect to survive beyond the biblical three score and ten years. It was therefore singularly appropriate to bring together those who were pioneers of modern anaesthesia so that the stories of what happened during the critical years could be recorded. At a conference on the History of Modern Anaesthesia, in Rotterdam on May 5–8 of this year, more than 150 contributors participated. In general presentations were concerned with people who had been active in the development of anaesthesia, with the way in which anaesthesia developed in certain specific locations (sometimes countries, sometimes cities) and with the drugs that became available over the years.

Not only was it desirable that the stories should be recorded—it was salutary for those who entered anaesthesia at a later date to learn something of the now forgotten difficulties which beset the pioneers.

The history of our own *Journal* found a place in the programme, as did an account of the UEMS and the World Federation of Societies of Anaesthesiologists. An opportunity was given to a nurse anaesthetist to present her view of their place in current practice and in the future, and the secretary of the Department of Anaesthetics at St Thomas's Hospital in London, who had served in this capacity for some 30 years, presented a "worm's eye" view of the specialty.

It is not possible within the compass of an editorial to do justice to the numerous papers which were read, but it is planned there will be a publication of the Proceedings of the Congress.

In the meantime we offer our congratulations to Dr J. Rupreht and his colleagues who conceived the idea of holding the conference and carried it through so successfully.

*A. R. Hunter*

# EDITORIAL

## INTRATHECAL BUPIVACAINE

In the United Kingdom only two local anaesthetic agents are presently supplied specifically for intrathecal administration, cinchocaine (Nupercaine) and mepivacaine (Carbocaine). Neither of these is ideal. Cinchocaine will not stand repeated autoclaving, and from time to time doubts have been raised regarding its continued production (Editorial, 1969; Horton, personal communication). Despite the excellent analgesia which this drug produces, not all patients require or will benefit from its prolonged action. Mepivacaine has a fairly short duration of action and is unsuitable for procedures which may last more than about 1 h (Dunn et al., 1963; Siker et al., 1966). The situation would be only slightly improved by the introduction of either of the agents most commonly used in North America, lignocaine and amethocaine (Tetracaine). When given intrathecally, lignocaine has an action similar to mepivacaine. Amethocaine must be mixed with another solution before injection and is not as stable in solution as other local anaesthetics.

Bupivacaine hydrochloride (Marcaine) has been available in the United Kingdom on 0.5% solution and has been widely used for all types of local anaesthesia other than spinal anaesthesia. Although not presented specifically for spinal anaesthesia, several reports have described its use for this purpose (Hengesbach and Matthes, 1977; Nolte et al., 1977; Lanz, Schellenberg and Theiss, 1979; Nolte and Stark, 1979; Cameron et al., 1981). Bupivacaine hydrochloride B.P. has a density of 0.998 at 37 °C (c.s.f. density 1.001) (Rosenberg and Goldberger, 1978; Rosenberg, 1980); this solution is therefore slightly hypobaric. These differences in density are not great enough to be of major clinical significance and in practice the solution behaves as a so-called isobaric solution, at least when administered in the volumes used for spinal anaesthesia. Intrathecal administration is accompanied by a high frequency of satisfactory spinal nerve blockade. In one review, over 95% of 5001 blocks were satisfactory for lower limb or perineal surgery (Nolte et al., 1977). The onset of sensory loss is rapid and is comparable to that produced by amethocaine (Lanz, Schellenberg and Theiss, 1979; Nolte and Stark, 1979). Most investigators agree that bupivacaine is less likely than amethocaine to produce complete motor block and that when it does so, the onset time is longer. However, insufficient motor block is seldom the sole reason for unsatisfactory operating conditions.

Local anaesthetics are usually prepared in higher concentrations for intrathecal use (e.g. 5% lignocaine) compared with their use at other sites. In the case of bupivacaine this causes several problems. A solution of 1% bupivacaine will precipitate when mixed with c.s.f. because a low pH is necessary to keep such concentrations in solution. The precipitate would redissolve when such a mixture was injected to the larger volume of c.s.f. present intrathecally and no case of permanent damage has been reported following the use of higher concentrations of bupivacaine. It would seem prudent, however, to use higher concentrations only if they afforded some clear advantage. Because comparatively weak solutions of bupivacaine are used intrathecally, larger volumes are required in order to administer a dose of the drug sufficient to produce a given degree of neural blockade. Some clinicians have used up to 5 ml of 0.5% bupivacaine, the most commonly used volume being between 3 ml and 4 ml. One study reported wide variability in the spread of this solution (Cameron et al., 1981) and this may be related to its strength. Wildsmith, McClure and Brown (1981) have shown that there is less variation in the spread of a given dose of amethocaine in isobaric solution when this is administered in a smaller volume and a higher concentration. Thus there may be some advantage in using isobaric solutions of 0.75% bupivacaine rather than 0.5%, but there is a lack of firm clinical evidence.

Interpretation of duration of action is complicated by the different methods of assessment which have been used. It appears that bupivacaine produces a block of similar but slightly shorter duration than amethocaine, sensory loss lasting for about 3–4 h in the legs and perineum. Ramaioli and Pagani (1972) reported durations of up to 8 h produced by bupivacaine 40 mg with adrenaline 0.5 mg with no apparent increase in adverse or toxic effects. The frequency of adverse effects and complications is similar to or less than that reported with other commercially available local anaesthetic agents (Kortum, Rossler and Nolte, 1979).

Bupivacaine is thus an excellent agent for spinal anaesthesia for perineal and lower limb surgery for those who wish to use an isobaric solution. It is highly reliable and has a duration of action between those of mepivacaine and cinchocaine. Where this solution fails, however, is when it is necessary to produce a block high enough for lower abdominal surgery (Chambers, Edstrom and Scott, 1981). In theory, greater cephalad spread could be obtained with the use of barbotage or injection at the second lumbar intervertebral space, but the former is not reliable or predictable and the latter unlikely to have a major effect.

Hyperbaric solutions have been produced by the addition of dextrose, in concentrations ranging from 5% to 10%, to overcome this problem. Although there is not much difference, in clinical practice, between hyperbaric solutions of different baricity, a dextrose concentration of around 8% is satisfactory (Moore, 1980; Chambers, Edstrom and Scott, 1981). Bupivacaine 0.5% in 8% dextrose consistently produces good spinal nerve block; the use of 0.75% bupivacaine in 8% dextrose offers no additional advantage (Chambers et al., 1982). Within the range 2–4 ml, increasing the volume of solution administered does not produce any change in spread, but produces a longer duration of action—an effect related to increased dosage. The duration of sensory loss is shorter than with the isobaric solution, sensory loss in the lower abdomen being of about 1.5–2 h duration. Presumably this is because a similar dose is used to block a greater mass of neural tissue. It would be interesting to know if volumes greater than 4 ml produced greater spread. If they did not, then the longer duration of action which such volumes would be expected to produce would be useful. Added vasoconstrictors cannot be relied upon to produce a significant increase in duration in individual cases (Chambers, Littlewood and Scott, 1982).

The introduction of hyperbaric bupivacaine will be a welcome addition to the limited range of agents currently available for intrathecal use in the U.K. Although the duration of action of a local anaesthetic depends as much on the dose administered as on the drug itself, this agent occupies a position between mepivacaine and cinchocaine. It should not be regarded as a replacement for the latter, the loss of which would be a significant setback for spinal anaesthesia in this country.

*W. Alastair Chambers*

REFERENCES

Cameron, A. E., Arnold, R. W., Ghoris, M. W., and Jamieson, V. (1981). Spinal analgesia using 0.5% bupivacaine plain. *Anaesthesia*, 36, 318.

Chambers, W. A., Edstrom, H. H., and Scott, D. B. (1981). Effect of baricity on spinal anaesthesia with bupivacaine. *Br. J. Anaesth.*, 53, 279.

—— Littlewood, D. G., Edstrom, H. H., and Scott, D. B. (1982). Spinal anaesthesia with hyperbaric bupivacaine: effect of dose and volume administered. *Br. J. Anaesth.*, 54, 75.

—— —— Scott, D. B. (1982). Spinal anesthesia with hyperbaric bupivacaine; effect of added vasconstrictors. *Anesth. Analg. (Cleve.)*, 61, 49.

Dunn, R. E., Gee, H. L., Carnes, M. A.; and Fabian, ●, ●. (1963). Spinal anesthesia with mepivacaine hydrochloride. *Anesth. Analg. (Cleve.)*, 42, 49.

Editorial (1969). *Anaesthesia*, 24, 155.

Hengesbach, B., and Matthes, H. (1977). Ausbreitung und Wirkungen von 0.5%igem Bupivacain nach subarachnoidaler Application. *Medsche Welt (Stuttg.)*, 28, 328.

Kortum, K., Rossler, B., and Nolte, H. (1979). Morbiditat nach Spinalanaesthesie. *Regional Anaesth.*, 2, 5.

Lanz, E., Schellenberg, B., and Theiss, D. (1979). Isobare Spinalanaesthesie mit Bupivacaine und Tetracain. *Regional Anaesth.*, 2, 25.

Moore, D. C. (1980). Spinal anesthesia: bupivacaine compared with tetracaine. *Anesth. Analg. (Cleve.)*, 59, 743.

Nolte, H., Schikor, K., Gergs, P., Meyer, J., and Stark, P. (1977). Zur frage der Spinanaesthesie mit isobarem Bupivacain 0.5%. *Anaesthesist*, 26, 33.

—— Stark, P. (1979). Die Dosis-Wirkungsrelation des isobaren Bupivacaine zur spinalanaesthesie. *Regional Anaesth.*, 2, 1.

Ramaioli, F., and Pagani, I. (1972). Nostra experienza sull 'impiego della bupivacaina all'1% iperbarica in 321 rachianestesie per interventi di chirurgica ortopedica e traumatologica. *Minerva Anest.*, 38, 1.

Rosenberg, H. (1980). Letter. *Regional Anaesth.*, 5, 21.

Rosenberg, H., and Goldberger, N. (1978). Density of local anesthetics: clinical implications. *Regional Anesth.*, **3**, 4.

Siker, E. S., Wolfson, B., Stewart, W. D., Pavilack, P., and Pappas, M. T. (1966). Mepivacaine for spinal analgesia. *Anesth. Analg. (Cleve.)*, **45**, 191.

Wildsmith, J. A. W., McClure, J. H., and Brown, D. T. (1981). Effect of injected volume on the spread of spinal anaesthesia. *Br. J. Anaesth.*, **53**, 1103.

*Br. J. Anaesth.* (1982), 54, 803

# EPIDEMIOLOGY IN ANAESTHESIA

## I: ANAESTHETIC PRACTICE OVER 20 YEARS

J. N. LUNN, S. C. FARROW, F. G. R. FOWKES, I. B. ROBERTSON AND P. SAMUEL

SUMMARY

The practice of anaesthesia and its outcome is compared, by means of the Cardiff Anaesthetic Record System, between two periods of 6 years, in which 53 541 and 108 878 anaesthetics were administered by the staff of one department. The proportion of emergency cases has increased from 10.6% to 18.7%, but the mortality in hospital has declined from 1 in 35 anaesthetics to 1 in 46.

Three previous accounts (Mushin et al., 1954; Mushin, Campbell and Ng, 1967; Lunn, 1976) have outlined the development since 1949 of the anaesthetic record system in Cardiff and have provided year-by-year comparisons. The main purpose of the present report is to describe the system which was in use between 1972 and 1977 and the data which were accumulated during that period. This comprises information about 108 878 anaesthetics. An opportunity was also taken to make comparisons with an earlier series of 53 541 anaesthetics acquired over a similar 6-year period from 1958 to 1963. Subsequent papers describe and explore the relationship between hospital mortality and preoperative condition, duration of anaesthesia, and cardiac arrest during operation.

### THE SYSTEM

Until 1972, the system was based on manual or machine sorting of Hollerith punch cards. From 1972 onwards the data have been stored on the ICL system 4-70 at University College, Cardiff. Data from the earlier period have been transferred recently to the same system.

Each time an anaesthetic is given to an inpatient, an anaesthetic sheet is completed by the patient's anaesthetist. This sheet is the only record of that patient's anaesthetic and is used as the source of data for both the computer system and the patient's clinical record. Therefore all patients having an anaesthetic are recorded by the system.

The record includes a large amount of descriptive information about the patient's condition before surgery, a record of events during the anaesthetic, including an arterial pressure chart, the events during the period of immediate recovery and the frequency of complications after surgery. The card is not self-coding and the next day the anaesthetic record clerk (of which there are three in different hospitals) transfers those items indicated by the anaesthetist by number to a series of boxes.

The anaesthetic record is allocated an individual number. The record is then returned to the anaesthetist for completion and the inclusion of postoperative complications. When this has been done the record clerk checks the sheet again, inserts numbers for the duration of hospital stay or the occurrence of death and sends it to the computer unit. The data for up to 160 boxes per patient are punched onto cards and then entered into the computer.

There is, in addition to the anaesthetic record card to which we have referred, a summary sheet which the anaesthetist completes at the time of the anaesthetic. This is retained in each patient's hospital clinical record and is available for any subsequent admission to hospital.

### *Validation*

When the data are entered into the computer a validity check is performed so that gross errors (for example, male operations upon female patients) are eliminated. Errors are listed and the anaesthetic record clerk notified, so that these sheets may be corrected and subsequently re-entered into the computer; at this stage the master file is created.

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The second part of the validation of the data for 1972–77 analysed in this paper is not carried out routinely, but when this current study was planned a unique opportunity arose, through the Job Creation Programme, to check the accuracy of the system. Five thousand random anaesthetic records were listed by number and the content of each was checked with the relevant information in the patient's hospital notes. The comparison was confined to a number of readily verifiable items of information on the summary anaesthetic sheet or the patient's documents (for example, premedication, diagnosis, use of certain drugs, duration of stay after operation, and the occurrence of death). The record clerks were shown by this process to be responsible for an error rate of 0.75%, the punch operators for 0.2% and the anaesthetists 5%.

## RESULTS

### *Age and sex of the patient populations*

Table I shows the percentage of females and males by age in both series. The two series show very little change in relation to age and sex structure. Compared with women, a higher percentage of males having anaesthetics are operated on in the youngest age range (0–14 yr), and in the older ranges 55 yr and over; women show a higher percentage than males in the 15–54 yr ranges. The overall female to male ratio was 1.4 :1 in the earlier series and 1.3 :1 in the later.

TABLE I. *Percentage age distribution of males and females having anaesthetics*

| Age (yr) | 1958–1963 Male(%) | 1958–1963 Female(%) | 1972–1977 Male(%) | 1972–1977 Female(%) |
|---|---|---|---|---|
| 0–14 | 17.1 | 6.6 | 17.1 | 7.4 |
| 15–24 | 10.2 | 12.0 | 12.1 | 15.7 |
| 25–34 | 9.7 | 15.4 | 10.3 | 20.4 |
| 35–44 | 10.6 | 17.1 | 9.8 | 15.9 |
| 45–54 | 12.1 | 16.4 | 13.5 | 15.0 |
| 55–64 | 14.8 | 13.3 | 16.6 | 10.8 |
| 65–74 | 12.7 | 10.3 | 14.2 | 8.9 |
| 75–84 | 7.5 | 5.8 | 5.7 | 4.7 |
| 85+ | 2.3 | 1.9 | 0.8 | 1.1 |
| Not known | 2.8 | 1.0 | — | — |
| All ages | 100 | 100 | 100 | 100 |

### *Sites of operation*

The number of operations increased from 53 541 to 108 878, principally as a result of the increase in the provision of surgical services with the opening of the University Hospital of Wales in 1972. The range of operative sites which are coded has broadened since the earlier series; the common sites are listed in table II. The changes include the separation of cystoscopy and radiological procedures from other sites. It should be noted, in addition, that much of the elective orthopaedic surgery in this Area is performed in a hospital which is not included in the record system and that in 1958–63 almost all the thoracic (pulmonary and cardiac) surgery was also outside the system.

TABLE II. *Percentage of principal operations performed at various sites*

| Operation site | 1958–1963 | 1972–1977 |
|---|---|---|
| Perineal | 26.1 | 21.9 |
| Lower abdomen | 17.7 | 15.9 |
| Upper abdomen | 9.7 | 7.0 |
| Leg | 6.7 | 8.0 |
| Nose and throat | 5.4 | 3.6 |
| Inguinal | 5.0 | 4.1 |
| Intracranial | 1.7 | 1.1 |
| Obstetrics | 1.8 | 1.9 |
| Cystoscopy | — | 7.6 |

### *Clinical assessment before operation*

Anaesthetists were able to indicate their overall clinical assessment of the patient's general condition before surgery in a similar manner to that of the Americal Society of Anesthesiologists classification (Dripps, Lamont and Eckenhoff, 1961). Table III shows how the surgical population has changed. There was a substantial increase in the 1972–77 series in the proportion of patients with major impairment, and of those who were in a bad or a moribund condition. This may be partly accounted for by the fact that the proportion of emergencies increased from 10.6% to 18.7% between the two series, or could possibly be a result of a change in the subjective impressions of anaesthetists.

TABLE III. *Relative distribution (%) of preoperative clinical assessments*

| Clinical assessment | 1958–1963 ($n$ = 53 541 = 100%) | 1972–1977 ($n$ = 108 878 = 100%) |
|---|---|---|
| Good | 43.5 | 47.4 |
| Minor impairment | 48.3 | 31.0 |
| Major impairment | 7.2 | 18.9 |
| Bad | 0.8 | 2.3 |
| Moribund | 0.09 | 0.3 |

### *Anaesthesia*

The practice of ***premedication*** has changed markedly (table IV). Whereas in the early series almost all anaesthetics included a premedication with atropine or hyoscine, in the later group this happened in only 75% of anaesthetics. This may partly be on account of the decline in the use of diethyl ether, but also because of the increasing awareness of the unpleasant subjective effects of these two drugs.

There has been a 30% reduction in the use of morphine in premedication and a substantial increase in the use of other drugs—mainly the sedatives and anxiolytics such as the butyrophenone and benzodiazepine drugs.

In the early series it is impossible now to determine much about the use of ***i.v. agents***, although 89.6% of anaesthetics included thiopentone or other barbiturate. In the later series, however, 82% of patients received thiopentone. The advent during this time of Althesin (used in 7.3% of anaesthetics) seems hardly to have affected the predominant position of thiopentone.

Anaesthetists seem to be using fewer ***inhaled agents*** (except for nitrous oxide) in the recent series than used to be their practice (table V). Halothane and particularly trichloroethylene are used much less frequently. (It should be noted that the use of one agent only in addition to nitrous oxide could be recorded for each anaesthetic in the 1958–62 series and anaesthetists recorded the main agent. There was no such limit in the later series.)

The overall use of ***muscle relaxants*** has declined only slightly from 68.9% to 65.4% of all anaesthetics administered. Table VI shows how the use of individual non-depolarizing relaxants and reversal agents has altered following the introduction of pancuronium. Compared with gallamine and tubocurarine, pancuronium is associated with a statistically significant increase in the use of postoperative ventilation in the recovery room (table VII).

Table VIII applies to the more recent series only; it is not possible to be certain of the frequency of combined or single use of relaxants in the early series. We do know, however, that 42.3% of patients who received relaxants received suxamethonium (or suxethonium, now withdrawn) in the early series, whereas 9.8% had suxamethonium in the recent series.

The ***analgesics*** fentanyl and phenoperidine were introduced into clinical practice during this time (1972–77) and table IX shows that their use during

TABLE IV. *Use of premedicant drugs—percentage of anaesthetics*

| | 1958–1963 (%) | 1972–1977 (%) |
|---|---|---|
| Antisialagogue | | |
| Atropine | 64.3 | 41.5 |
| Hyoscine | 35.0 | 33.2 |
| No antisialagogue | 0.8 | 25.1 |
| Analgesic/sedative | | |
| Morphine | 41.1 | 11.7 |
| Papaveretum | 33.6 | 36.7 |
| Pethidine | 9.0 | 10.9 |
| None | 15.2 | 21.4 |
| Others | 1.1 | 19.3 |

TABLE V. *Use of specific inhalation agents—percentage of anaesthetics*

| Agent | 1958–1963 (%) | 1972–1977 (%) |
|---|---|---|
| Nitrous oxide | 94.3 | 91.2 |
| Halothane | 72.3 | 64.1 |
| Trichloroethylene | 21.3 | 7.1 |
| Cyclopropane | 1.6 | 0.4 |
| Diethyl ether | 5.0 | 0.6 |
| Others | 3.9 | 0.3 |

TABLE VI. *Relative use of certain non-depolarizing relaxants*

| | 1958–1963 (%) | 1972–1977 (%) |
|---|---|---|
| Non-depolarizing relaxant | ($n$ = 21 730) | ($n$ = 45 961) |
| Gallamine | 73.2 | 7.9 |
| Tubocurarine | 26.8 | 10.6 |
| Pancuronium | — | 78.9 |
| Other | — | 2.5 |
| Total non-depolarizing relaxants | 100 | 100 |
| Total reversal agents (% recipients of relaxants) | 62.3 | 87.6 |

TABLE VII. *Requirement for postoperative ventilation after pancuronium, tubocurarine or gallamine.* $^{*}\chi^2 = 4.17$; *d.f.* $= 1$; $P < 0.05$. $^{**}\chi^2 = 10.56$; *d.f.* $= 1$; $P < 0.005$

| After use of | Ventilation | No ventilation |
|---|---|---|
| Pancuronium | 234 | 36047 |
| Tubocurarine | 19 | 4856* |
| Gallamine | 7 | 3635** |

TABLE VIII. *Relative use of muscle relaxants in 1972–1977*

| | Percentage of all relaxants ($n = 71\,234$) |
|---|---|
| Suxamethonium alone | 35.8 |
| and tubocurarine | 4.5 |
| and gallamine | 3.1 |
| and pancuronium | 35.7 |
| and other | 0.7 |
| Tubocurarine alone | 2.3 |
| Gallamine alone | 2.0 |
| Pancuronium alone | 15.0 |
| Other | 0.8 |
| Any single or combined relaxant | 100 |

TABLE IX. *Choice of analgesic by grade of anaesthetist—numbers of anaesthetics*

| Anaesthetist | Fentanyl | Phenoperidine | Morphine | Pethidine |
|---|---|---|---|---|
| Consultant | 4320 | 860 | 1218 | 859 |
| Senior registrar | 3929 | 1170 | 769 | 190 |
| Registrar | 7881 | 820 | 1459 | 745 |
| Senior House Officer | 2233 | 151 | 190 | 270 |
| Medical/ Clinical assistants | 182 | 134 | 21 | 55 |

anaesthesia is much more common than that of morphine and pethidine. However, this is associated with the grade of anaesthetist and the trainees more commonly use these drugs than do the consultants ($\chi^2 = 2621$; d.f. $= 12$; $P < 0.00001$).

*Spinal and extradural anaesthesia*

In 1958–63 0.3% of anaesthetics were spinal or extradural, compared with 2.3% in 1972–77. The early period was in the aftermath of the medico-legal case of Wooley and Roe and shows the effect which that case may have had on anaesthetic practice.

*I.v. fluids and monitoring*

The use of i.v. fluids has apparently increased from 11.3% to 36.1% of anaesthetics, although that of blood transfusion does not seem to have changed—9.4 and 10.6% respectively in the two series.

The arterial pressure was measured indirectly during anaesthesia in the 1972–77 series in 82% of anaesthetics and the electrocardiograph was used in 53%. Monitoring *instruments* were not used in 10% and ventilation was measured in 30% of anaesthetics.

*Incidents during anaesthesia*

An incident is defined as an occurrence of sufficient importance to necessitate a change in the management of the anaesthetic; such incidents occurred in 45% of anaesthetics in the early series and in 19.8% of the later series.

*Duration of anaesthesia*

Figure 1 shows the cumulative percentage of duration of anaesthesia. In both series, approximately two-thirds were completed by 1 h and only 3% took longer than 3 h.

*Postoperative hospital stay*

Table X confirms other data that the postoperative hospital stay of surgical patients has declined. In particular, whereas 16.7% of patients stayed in hospital less than 4 days after operation in 1958, in 1977 40.7% were discharged in less than 4 days. This was a result of changes not only in anaesthetic practice but also in surgical and other practices.

TABLE X. *Postoperative stay in hospital (cumulative %)*

| Days | 1958–1963 | 1972–1977 |
|---|---|---|
| 0–3 | 16.7 | 40.7 |
| 4–6 | 38.8 | 58.1 |
| 7–13 | 68.5 | 84.1 |
| 14+ | 83.5 | 92.2 |

*Death following surgery*

The overall death rate (irrespective of its timing or its cause) in hospital has declined from 2.86 to 2.19 per 100 anaesthetics. This figure may reflect changes in anaesthetic practice as well as the surgical management of patients. Other papers in this series will deal with this matter in detail. Table XI shows the percentage distribution of the day of postoperative death: almost two-thirds had occurred within 2 weeks of operation.

In the 1958 series 31.2% of the deaths had occurred within the first 3 days compared with 26.0% on the later series ($\chi^2 = 12.99$; d.f. $= 1$; $P < 0.0005$).

*Preoperative conditions (1972–1977)*

From a total of 107 individual preoperative condi-

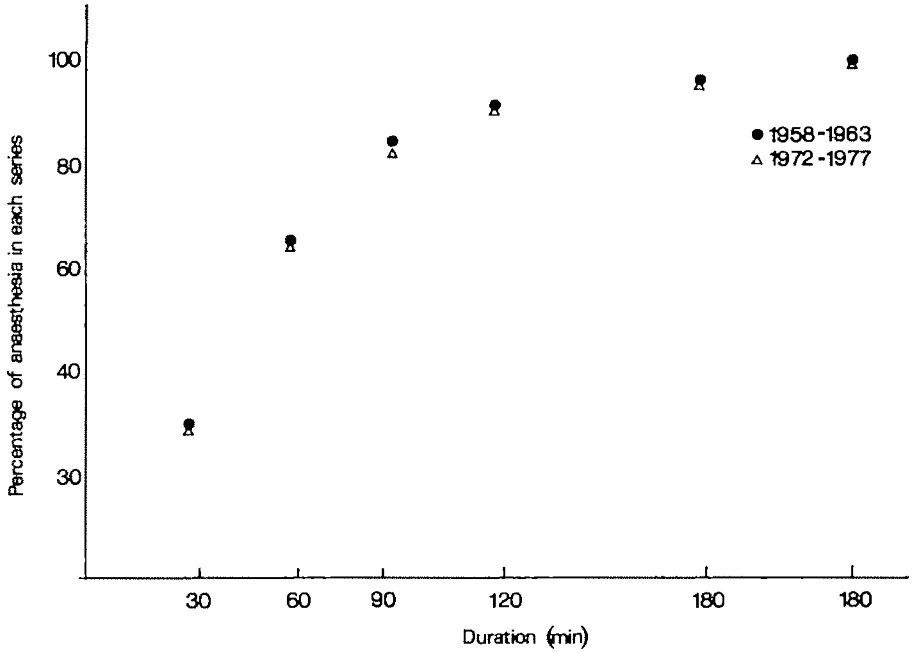

FIG. 1. Cumulative percentage of anaesthetics by duration of operation.

TABLE XI. *Day of postoperative death. Percentage of patients dying at each time*

| Day | 1958–1963 (*n* = 1532) | 1972–1977 (*n* = 2391) |
|---|---|---|
| Theatre | 2.1 | 4.3 |
| Recovery room | — | 1.1 |
| 0 | 7.6 | 4.2 |
| 1–3 | 21.5 | 16.4 |
| 4–6 | 13.4 | 17.1 |
| 7–13 | 20.3 | 20.0 |
| 14–20 | 10.7 | 15.2 |
| 21+ | 24.1 | 21.6 |

TABLE XII. *Frequency of preoperative conditions*

| | % Anaesthetics |
|---|---|
| Chronic lower respiratory tract infection | 7.4 |
| Emphysema, pneumoconiosis or pulmonary fibrotic lesion | 2.1 |
| Angina | 1.9 |
| Ischaemic heart disease | 3.9 |
| Pregnant (but non-obstetric operation) | 0.3 |
| Renal failure (acute and chronic) | 0.6 |
| Excessive alcohol intake | 1.4 |
| Obesity | 5.0 |
| Weight loss | 1.8 |
| Diabetes (controlled and uncontrolled) | 1.3 |
| Impairment of health by surgical diagnosis | 9.8 |
| Allergies | 2.5 |
| Relevant deformities | 0.9 |
| Previous untoward incidents during anaesthesia | 0.25 |

tions, the anaesthetist could select up to 10 different items to be recorded. On the average, just over two were recorded per anaesthetic. Some of the common ones are listed in table XII, but it is clear that they are not all of equal import.

In table XIII, all the preoperative conditions have been grouped together by system. Some of the groups have an unexpectedly high frequency. In particular, the "central nervous system" group included an item "marked apprehension" and this accounts for 48% of the occasions when this system was indicated. The "iatrogenic" group included an indication of previous anaesthetic and the "other" group included "impairment of general health" which accounted for 56% of the occasions on which the system was indicated.

TABLE XIII. *Frequency of preoperative conditions by system (1972–1977). (More than one condition could be recorded.) *48% apprehension; **56% impairment of general health by surgical diagnosis*

| | % Anaesthetics |
|---|---|
| Respiratory | 20.5 |
| Cardiovascular | |
| symptoms/signs | 9.2 |
| diagnosis | 13.7 |
| Gynaecological/obstetric | 2.0 |
| Central nervous* | 16.3 |
| Urinary | 2.5 |
| Alimentary | 5.2 |
| Metabolic and endocrine | |
| signs | 11.5 |
| diagnoses | 2.9 |
| Iatrogenic | 30.9 |
| Other** | 17.3 |

*Previous general anaesthetic*

In the later series it was possible to record the occurrence of previous general anaesthetics. In 2.7% of cases it was recorded that there had been an anaesthetic given to the same patient in the period less than 4 weeks before the present anaesthetic; 3.4% of patients had had an anaesthetic up to 6 months before and 7.3% of patients had had an anaesthetic between 6 months and 5 years before. Thus, in this particular population the problem of repeated anaesthetics does not seem to be a common one.

## DISCUSSION

Analysis of information from records of anaesthesia has seldom been attempted in the United Kingdom on this scale before and we are convinced that, whilst much of the information contained in this report may be appreciated on an individual basis and even be commonplace, nevertheless there is a need for it to be documented. Furthermore, if there are conclusions to be drawn they may be made with some confidence because of the large numbers reported and because of the low error rate. The fact that anaesthetists are no different from other doctors in relation to accurate record keeping need not be the occasion for surprise, merely for disappointment.

It is clear that the record and computer systems used here are powerful tools for epidemiological research and capable of many applications. In particular, this system has already been used as a springboard for clinical research (Rosen and Mushin, 1967) and could easily be utilized for clinical audit. However, it is expensive and time-consuming for anaesthetists and clerical staff. The record has therefore been revised to reduce the time necessary for its completion: the rationale of this is described elsewhere (Lunn and Vickers, 1982).

The change in surgical practice which has followed advances in medicine and pharmacology is exemplified by the increased admission of seriously ill patients for surgery. Despite this fact the hospital mortality has decreased to 1 in 46 anaesthetics. Specialist hospitals are likely to have a greater proportion of these ill patients than district general hospitals. The increased number of emergency operations may reflect pressure for operating time during the day which is relieved by the designation, wrongly in our view, of an operation as an emergency which is then performed when perhaps neither facilities nor skilled staff are easily available.

We are disappointed to note that the records state that no monitoring instruments were used at all in 10% of anaesthetics and that i.v. fluids were not given more frequently. It is easy to omit routine information from the record and this may be the explanation but, if so, it only emphasizes the necessity to ensure that any record is as complete as possible before conclusions about practice are drawn.

The association between the use of pancuronium and the necessity for postoperative ventilation of the lungs in the recovery period is interesting. The same unpublished observation was made in the early period of use of the drug on the basis of the anaesthetic records for 1 year and this study confirms the preliminary observation. Pancuronium may have been used preferentially at the time of these anaesthetics for poor-risk or emergency cases because it was recently introduced and was then believed to be free of cardiovascular effects. Prophylactic postoperative ventilation and the use of potent narcotics had also become popular in the interim and facilities for intensive care more available. We do not suggest that there is a causal relationship between these two events, but the observation may serve to alert clinicians that such a possibility exists.

It is not surprising that trainees tend to use drugs which have been recently introduced but the evidence of patient benefit seems to be less obvious to their trainers! This may be a matter of considerably wider interest than that of anaesthetists and could be investigated in other areas of medical practice.

Readers may be surprised that we have made no comment about complications after operation. This important matter, we have found over the years, is not studied satisfactorily through the anaesthetic record system. There are a number of reasons for this—the multifactorial nature of their causation, in particular their temporal relationship to the anaesthetic and the anaesthetist's postoperative visits, all of which combine to preclude accurate recording. In these studies we have therefore concentrated on postoperative information which we have reason to believe is well recorded, namely postoperative stay and death, which are noted by the clerical staff employed in the system.

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### REFERENCES

Dripps, R. D., Lamont, A., and Eckenhoff, J. E. (1961). The role of anesthesia in surgical mortality. *J.A.M.A.*, 178, 261.

Lunn, J. N. (1976). A ten-year survey of anaesthetic practice in Cardiff. Excerpta Medica International Congress Series No. 399 *Anaesthesiology*. Proceedings of the VI World Congress of Anaesthesiology, Mexico City, p.51.

——Vickers, M. D. A. (1982). A new anaesthetic record card. *Anaesthesia*, 37, (in press).

Mushin, W.W., Campbell, H., and Ng, W.S. (1967). The pattern of anaesthesia in a general hospital. *Br. J. Anaesth.*, 39, 323.

——Rendell-Baker, L., Lewis-Faning E., and Morgan, J. H. (1954). The Cardiff Anaesthetic Record System. *Br. J. Anaesth.*, 26, 298.

Rosen, M., and Mushin, W. W. (1967). The value of an organised anaesthetic recording system in clinical trials. *Br. J. Anaesth.*, 39, 320.

## EPIDEMIOLOGIE EN ANESTHESIE
## I: PRATIQUE DE L'ANESTHESIE SUR PLUS DE 20 ANS

### RESUME

La pratique de l'anesthésie et ses résultats sont comparées grâce au système de fichier anesthésique de Cardiff au cours de deux périodes de 6 ans pendant lesquelles 53 541 et 108 878 anesthésies ont été délivrées par l'équipe d'un même département. La proportion des urgences a augmenté de 10,6% à 18,7% mais la mortalité à l'hôpital a diminué de 1 pour 35 anesthésies à 1 pour 46.

## EPIDEMIOLOGIE IN DER ANÄSTHESIE
## I: ANÄSTHESIOLOGISCHE PRAXIS WÄHREND 20 JAHREN

### ZUSAMMENFASSUNG

Anästhesiologische Erfahrungen und ihre Ergebnisse werden mit Hilfe des "Cardiff Anaesthetic Record Systems" zwischen zwei Perioden von 6 Jahren verglichen, in denen 53 541 und 108 878 Narkosen durch den Staff einer Abteilung durchgeführt wurden. Der Anteil der Notfälle nahm von 10,6% auf 18,7% zu, während die Todesfälle im Krankenhaus von 1 auf 35 Narkosen zu 1 auf 46 Narkosen abnahmen.

## LA EPIDEMOLOGIA EN LA ANESTESIA
## I-LA PRACTICA ANESTESICA DURANTE 20 AÑOS

### SUMARIO

Se utiliza el Sistema de Registros Anestésicos de Cardiff para la comparación de dos periodos de 6 años, relativos a la anestesia y a su resultados, durante los que se administraton 53.541 y 108.878 anestesias por parte del personal de un departamento. La proporción de casos de urgencia ha aumentado desde el 10,6% hasta el 18,7%, pero el índice de mortalidad en el hospital ha declinado desde 1 por cada 35 anestesias hasta 1 por cada 46.

*Br. J. Anaesth.* (1982), 54, 811

# EPIDEMIOLOGY IN ANAESTHESIA

# II: FACTORS AFFECTING MORTALITY IN HOSPITAL

S. C. FARROW, F. G. R. FOWKES, J. N. LUNN, I. B. ROBERTSON AND P. SAMUEL

## SUMMARY

The hospital mortality following 108 878 anaesthetics in Cardiff between 1972 and 1977 has been analysed. There was a total of 2391 deaths, giving a crude mortality rate of 2.2 per 100 patients. Data are presented on several important variables that influence mortality. These include age, sex, preoperative clinical assessment score, preoperative condition, site of operation, operation, whether elective or emergency and duration of anaesthesia.

In the past many attempts have been made to study the cause of death in surgical patients. Some of these have been based on Coroners reports and have concentrated on immediate deaths or deaths within 48 h of the operation (Edwards et al., 1956; Clifton and Hotten, 1963; Rashad et al., 1965; Holland, 1970; Bodlander, 1975). Although these studies are useful in considering deaths where anaesthesia is thought to be responsible they miss the later postoperative deaths.

The first paper in this series compared the anaesthetic records of the 1958–63 patients and those of 1972–77. Over this period the number of anaesthetics approximately doubled and the proportion of emergencies increased from 10.6% to 18.7%. There was a substantial increase in the later series in the proportion of patients with major impairment before operation. Nevertheless the crude mortality rate decreased from 2.9 to 2.2 per 100 patients.

This paper considers the mortality of patients in hospital in the 1972–77 series in detail. Factors that have been considered include age, sex, the preoperative clinical assessment score and the preoperative condition. Surgical and anaesthetic factors have included the site of operation, the operation itself, whether the operation was elective or an emergency and the duration of anaesthesia. No specific attempt has been made to assign the cause of death to anaesthesia or surgery. Factors have been dealt with as if they were single independent variables. A multivariate analysis will be the subject of a later paper.

## METHOD

The first, accompanying, paper in this series described the anaesthetic data system which has been operating in Cardiff since 1949, and gave details of the method of data acquisition, retrieval and analysis. Validation was carried out in two stages: the first was a basic computer validation to exclude information outside a specified range; the second involved a check of 5000 records to compare the computer printout of the anaesthetic data with the patient's own medical record notes. The record clerks were shown by this process to be responsible for an error rate of 0.75%, the punch operators 0.2% and the anaesthetists 5%.

## RESULTS

There were 2391 deaths during or following 108 878 anaesthetics giving a crude mortality rate of 2.2 per 100 patients.

Of these 2391 deaths 102 were in theatre, 27 in the recovery room and 2262 in the ward. The ward deaths were further subdivided by time and figure 1 shows the cumulative percentage deaths of those dying in hospital by time. Approximately 50% of those dying in hospital die within the first 7 days.

### *Age and sex*

Table I shows the male and female mortality rates by age. The overall male mortality rate was 2.7 compared with 1.8 for females, giving an overall male:female mortality ratio of 1.5:1. This increased mortality rate in males was at its greatest in the 15–24 yr age group (ratio 2.90:1) and in the

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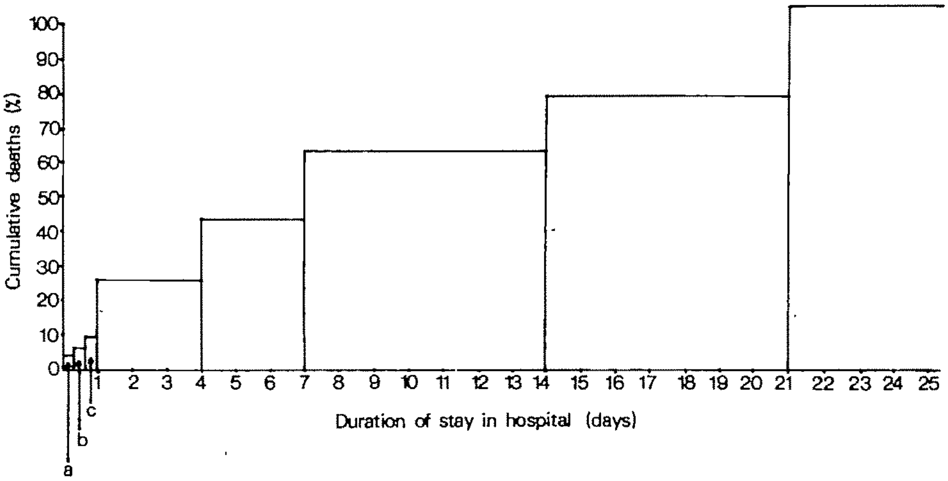

FIG. 1. Cumulative percentage of deaths in hospital by time in days. a = Deaths in theatre; b = deaths in recovery room; c = deaths in ward during first 24 h.

25–44 yr age group (3.04:1). In older age, 65 yr and more, the ratio was reversed.

Mortality rates for males and females were similar in the 0–14 yr age group and were higher than in early adult life. It would seem likely that this increased mortality is accounted for by operations in the neonatal period, especially for procedures associated with congenital abnormalities.

### *Clinical assessment score before operation*

Table II shows the mortality rate by preoperative clinical assessment score. This assessment, which is made by the anaesthetist on examining the patient before surgery, is a subjective appraisal and takes into account a number of patient risk factors including age, preoperative conditions such as cardiovascular disease or impaired respiratory function as well as the type of operation to be performed and whether it is elective or emergency. For convenience we refer to this assessment as a score (category 1 = good; 2 = minor impairment; 3 = major impairment; 4 = bad and 5 = moribund).

The mortality rate varied from 0.3 per 100 patients for those classified as good to 57.8 per 100 for those classified as moribund. The number of operations performed on patients assessed as category 1, 2 or 3 was 106 003 or 97.4% of all operations and in these there were 1489 deaths, an overall mortality rate of 1.4 per 100 patients.

### *Condition before operation*

Table III lists a number of preoperative conditions recorded by anaesthetists as a result of preoperative visits. Cardiac failure before operation was associated with 186 deaths from 1175 patients, giving a mortality rate of 15.8 per 100 patients. Impaired renal function was associated with 84 deaths from 779 cases, giving a mortality rate of 10.8

TABLE I. *Mortality rate by age and sex*

| | Males | | | Females | | | |
|---|---|---|---|---|---|---|---|
| Age (yr) | No. deaths | Total | Mortality rate (%) | No. deaths | Total | Mortality rate (%) | Mortality ratio male:female |
| 0–14 | 105 | 8041 | 1.3 | 59 | 4601 | 1.3 | 1.02:1 |
| 15–24 | 46 | 5695 | 0.8 | 27 | 9683 | 0.3 | 2.90:1 |
| 25–44 | 121 | 9488 | 1.3 | 94 | 22411 | 0.4 | 3.04:1 |
| 45–64 | 428 | 14174 | 3.0 | 331 | 15925 | 2.1 | 1.45:1 |
| 65+ | 578 | 9749 | 5.9 | 612 | 9111 | 6.7 | 0.88:1 |
| All ages | 1268 | 47147 | 2.7 | 1123 | 61731 | 1.8 | 1.48:1 |

TABLE II. *Mortality rate by clinical assessment*

| | No. deaths | No. patients in category | Mortality rate (%) |
|---|---|---|---|
| Clinical assessment | | | |
| 1 = good | 173 | 51668 | 0.3 |
| 2 = minor impairment | 288 | 33744 | 0.9 |
| 3 = major impairment | 1082 | 20591 | 5.3 |
| 4 = bad | 662 | 2553 | 25.9 |
| 5 = moribund | 186 | 322 | 57.8 |
| Total | 2391 | 108 878 | 2.2 |

TABLE III. *Mortality by selected preoperative condition*

| | No. deaths | No. ops | Mortality rate (%) |
|---|---|---|---|
| Cardiac failure | 186 | 1175 | 15.8 |
| Impaired renal function | 84 | 779 | 10.8 |
| Vomiting | 154 | 1529 | 10.1 |
| Previous general anaesthetic | 219 | 3014 | 7.3 |
| Angina, arteriosclerosis or ischaemic heart disease | 544 | 7776 | 7.0 |
| Impairment of general health by surgical diagnosis | 631 | 10681 | 5.9 |
| Diabetes | 82 | 1452 | 5.7 |
| Chronic lower respiratory tract infection | 408 | 8060 | 5.1 |
| Obesity | 116 | 5434 | 2.1 |
| No preoperative condition | 206 | 43483 | 0.5 |

per 100 patients and ischaemic heart disease with 544 deaths from 7776 cases, giving a mortality rate of 7.0 per 100 patients. The mortality rate for patients with no defined condition before surgery was 0.5 per 100 patients.

*Site of operation*

More than one operation and site was possible for each patient, but only the principal operation site has been presented in the following analysis. In the particular classification used there were 25 different sites. These varied from the specific, such as eye and thyroid, to the more general such as head and neck (excluding thyroid), upper abdomen and lower abdomen. Table IV shows that the most frequent sites for operation were perineal, lower abdomen, leg, cystoscopy and upper abdomen. Sites associated with the largest absolute number of deaths were upper abdomen (501), lower abdomen (481), leg (328) and intrathoracic (231). Sites carrying the highest mortality rates were intracranial (9.7%), intrathoracic (8.6%), upper abdomen (6.6%) and head and neck, excluding thyroid (6.4%).

*Operation*

Only the principal operation code has been analysed. Table V lists those operations with the highest mortality. With the exception of laparotomy, for which there were 3658 patients with a mortality of 14.2 per 100 patients, all the operations carrying a high mortality were performed relatively infrequently. Tracheotomy and laryngectomy had a mortality rate of 37.8 per 100 patients and amputation through thigh 20.6 per 100 patients. Table VI shows the mortality rates associated with the commoner operations. In general it can be seen that the common operations carry a low risk, for example dilatation and curettage (8000 operations) at a mortality rate of 0.1 per 100 patients and cystoscopy (7483 operations) at a mortality rate of 0.6 per 100 patients. The two commom operations associated with the greatest mortality rates were laparotomy (14.2 per 100 patients) and reduction and internal fixation of fracture (7.1 per 100 patients).

*Elective and emergency operations*

There were 1348 deaths during and following 89 032 elective operations, giving a crude mortality

TABLE IV. *Mortality by site of operation*

| Site | No. deaths | No. ops | Mortality rate (%) |
|---|---|---|---|
| Abdominal wall | 27 | 679 | 4.0 |
| Arm | 12 | 3376 | 0.4 |
| Bronchoscopy, laryngoscopy and oesophagoscopy | 117 | 3162 | 3.7 |
| Chest wall | 19 | 3596 | 0.5 |
| Cystoscopy | 64 | 8296 | 0.8 |
| Ear | 0 | 1546 | 0.0 |
| Eye | 4 | 4686 | 0.1 |
| Head and neck (not thyroid) | 217 | 3376 | 6.4 |
| Inguinal | 30 | 4539 | 0.7 |
| Intracranial | 124 | 1273 | 9.7 |
| Intrathoracic | 231 | 2693 | 8.6 |
| Kidney region | 36 | 1031 | 3.5 |
| Leg | 328 | 8675 | 3.8 |
| Lower abdomen | 481 | 17351 | 2.8 |
| Mouth and dental | 10 | 4791 | 0.2 |
| Nose and throat | 32 | 4008 | 0.8 |
| Obstetric Caesarean | 0 | 2043 | 0.0 |
| Obstetric not Caesarean | 0 | 171 | 0.0 |
| Perineal | 47 | 23945 | 0.2 |
| Radiological investigation | 75 | 806 | 9.3 |
| Spine and back | 29 | 1564 | 1.9 |
| Thyroid | 2 | 993 | 0.2 |
| Upper abdomen | 501 | 7649 | 6.6 |
| Other | 5 | 213 | 2.4 |

TABLE V. *Operations with high mortality rates*

| Operation | No. deaths | No. ops | Mortality rate (%) |
|---|---|---|---|
| Tracheotomy and laryngectomy | 109 | 288 | 37.8 |
| Amputation through thigh | 34 | 165 | 20.6 |
| Craniotomy | 125 | 704 | 17.8 |
| Operations on abdominal vessels | 36 | 195 | 18.5 |
| Laparotomy | 518 | 3658 | 14.2 |
| Gastroenterotomy | 17 | 128 | 13.3 |
| Transplantation of kidney | 22 | 185 | 11.9 |
| Repair abdominal wall | 20 | 177 | 11.3 |
| Heart valve replacement | 51 | 473 | 10.8 |
| Repair perforated duodenal ulcer | 11 | 103 | 10.7 |
| Cerebral arteriography | 61 | 592 | 10.3 |

TABLE VI. *Mortality rates for common operations*

| Operation | No. deaths | No. ops | Mortality rate (%) |
|---|---|---|---|
| Dilatation and curettage | 6 | 8000 | 0.1 |
| Cystoscopy | 42 | 7483 | 0.6 |
| Laparotomy | 518 | 3658 | 14.2 |
| Repair of inguinal hernia | 15 | 3513 | 0.4 |
| Emergency appendicectomy | 7 | 3282 | 0.2 |
| Other termination of pregnancy | 2 | 2769 | 0.1 |
| Hysterectomy | 2 | 2634 | 0.1 |
| Cholecystectomy | 21 | 2552 | 0.8 |
| Reduction and internal fixation of fracture | 160 | 2262 | 7.1 |

rate of 1.5 per 100 patients. After 19 774 emergency operations 1038 deaths occurred, giving a crude mortality rate of 5.3 per 100 patients. The overall increased relative risk of emergency over elective was approximately 3.5:1.

### *Duration of anaesthesia*

Figure 2 shows the mortality rate by duration of anaesthesia. It varies from 0.5 per 100 patients in whom the duration of anaesthesia was less than 30 min to 22.6 per 100 patients for procedures lasting longer than 8 h. A total of 98 191 procedures was completed in under 2 h, which was 90% of all cases analysed. The overall mortality rate in these patients was 1.6 per 100 patients. In the period 2–6 h there were 703 deaths from 9978 patients (mortality rate 7.05 per 100 patients) and in the period 6–10 + h there were 102 deaths from 709 patients (mortality rate of 14.4 per 100 patients).

## DISCUSSION

Studies of deaths following anaesthesia and surgery have a long and varied history. The possible danger of a particular anaesthetic agent has been one of the principal motivating factors. The first instance of

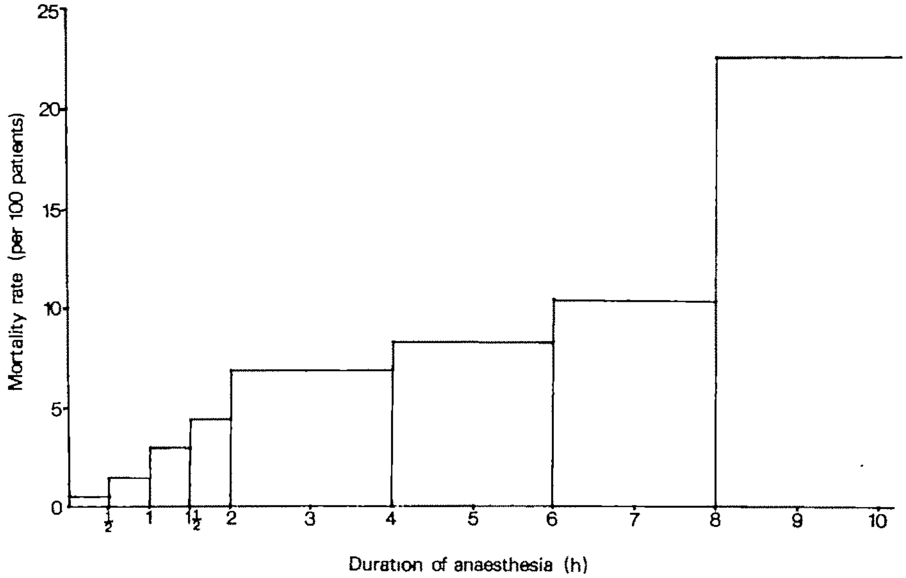

FIG. 2. Mortality rate (per 100 patients) by duration of anaesthesia (h).

this was in 1875 when chloroform, ether and nitrous oxide were investigated. Although the subsequent report questioned the danger of using chloroform without an inhaler, the general conclusion seemed to be that the data systems were inadequate to answer questions on the cause of death. More recently the National Halothane Study (Bunker et al., 1969) reviewed 853 000 operations in 35 institutions. The study made possible a comprehensive review of deaths following anaesthesia and surgery.

Perhaps the most important factor in the now frequent evaluation of practice has been the development of medical information systems and the increased capacity for data storage and retrieval. A historical review of these developments in anaesthetic record systems has been provided by Hallén (1973). One of the earlier studies reviewed a vast collection of data from large University Hospitals in the United States (Beecher and Todd, 1954) and described the outcome of 599 548 anaesthetics in 10 institutions between 1948 and 1952.

In Australia the experience in one large hospital was reviewed over a 10-yr period (Clifton and Hotten, 1963). From 1952 to 1962, 205 640 operations and anaesthetics were analysed. Deaths associated with anaesthesia were defined as those occurring during anaesthesia, those in which the patient failed to regain consciousness following anaesthesia, and those occurring as a direct result of anaesthesia, according to specific criteria. The total number of deaths analysed using this definition was 162. The experience of the next decade was again reviewed (Bodlander, 1975) and during this period there were 408 deaths from 211 130 anaesthetics.

A more recent study (Hovi-Viander, 1980) looked at deaths associated with anaesthesia in Finland in 1975. Deaths were abstracted from the Patients Departure Register kept by the National Board of Health and were drawn from 338 934 anaesthetics in 100 hospitals. Associated deaths were defined as those dying within 3 days (473), those suffering cardiac arrest during anaesthesia but dying more than 3 days later (five) and later deaths where anaesthesia was held to be responsible (148).

In the United Kingdom national studies are in progress to review the causes of death in patients dying within 6 days of anaesthesia. Such confidential enquiries attempt to determine the degree of responsibility of the anaesthetic process in the causation of death (Lunn and Mushin, 1981).

The present Cardiff study is based on all deaths in hospital during the admission when the anaesthetic and surgical intervention took place. The description of 2391 deaths represents one of the larger series available. It is also an attempt to describe the results of surgical and anaesthetic practice in a defined Health Authority Area where a group of major hospitals provide care to the population of Cardiff and its immediate neighbours. The resident population is approximately 400 000, although for some of the specialist services the Regional nature of the service draws on a wider population in South Wales.

That mortality rates increase with age is well established (Scott, 1961; Bunker et al., 1969; Holland, 1970; Marx, Mateo and Orkin, 1973). This may be a result of the presence of coexisting preoperative conditions and of the type of operation being performed. There is a lower percentage of elective surgery in the elderly and an increase in surgery for carcinoma, which carries a higher mortality. There is also the likelihood of surgical selection which may tend to favour the major rather than minor operations.

The all-age male:female mortality ratio was 1.5:1. The age-specific mortality rates showed an unexpected reversal of the male:female ratio in older age. It does appear that women are at greater risk than men of dying following anaesthesia and operation if older than 65 years of age. A separate study of the Registrar General's mortality data for England and Wales (O.P.C.S., 1975) showed a male:female mortality ratio of 1.3 in children, increasing to 2.0 in middle age and decreasing to approximately 1.3 in old age. The male:female population ratio in Wales in 1975 for those over 65 yr was approximately 0.64 and of those undergoing surgery in South Glamorgan the ratio was approximately 1. It does appear that men are receiving a disproportionate number of operations compared with women, but that the surgical mortality rate in older women is greater. This may be related to the type of operation performed in males and females. For example, cystoscopy is more common in males and reduction and internal fixation of fracture more common in females.

The early work on the grading of patients by clinical assessment scores before operation was described by Saklad (1941). Feigal and Blaisdell (1979) compared the mortality rates during the 6 weeks following surgery in patients with different preoperative clinical assessment scores. These data were taken from the National Halothane Study (Bunker et al., 1969) and are based on 856 000 anaesthetic procedures. The mortality rates per 100 patients were as follows: assessment score I = 0.18, II = 1.4, III = 5.4, IV = 12.4 and V = 27.3.

Elective and emergency procedures, although not free of some difficulties in definition, do allow for some comparison with other published work. The 48-h mortality rates in 68 388 cases were compared by Vacanti, Van Houten and Hill (1970). They looked at the mortality for each of the preoperative clinical assessment scores. In this series the emergency to elective ratio was grade I = 2.3, grade II = 2.1, grade III = 2.4, grade IV = 1.1 and grade V = 1.2. The National Halothane Study combined the results of elective emergency surgery with the question of low, medium or high risk. For elective surgery the results were: low risk 0.23, medium risk 2.2, and high risk 10.0. This gives an overall elective mortality rate of 1.9 compared with 1.5 from our own results (Feigal and Blaisdell, 1979).

The duration of anaesthesia is another area where it is difficult to identify the combination of different factors. The type of surgery, experience of the surgeon and unexpected complications, all influence the duration of anaesthesia. In one series in the aged (Cogbill, 1967) the mortality rates did not seem to be related to the length of anaesthesia. Although the numbers were small (529 cases and 67 deaths), all the operations were for patients undergoing six specific abdominal operations. On the other hand, the physiological disadvantages of prolonged anaesthesia need to be considered and these have been reviewed (Vandam, 1965).

The analysis of 2391 deaths with a crude mortality rate of 2.2 per 100 patients helps describe the importance of several underlying factors. This type of analysis is not entirely satisfactory because it fails to control simultaneously for the different variables, and subsequent papers will look at this problem in more detail.

## ACKNOWLEDGEMENTS

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## REFERENCES

Beecher, H. K., and Todd, D. P. (1954). A study of the deaths associated with anaesthesia and surgery. *Ann. Surg.*, **140**, 2.

Bodlander, F. M. S. (1975). Deaths associated with anaesthesia. *Br. J. Anaesth.*, **47**, 36.

Bunker, J. P., Forrest, W. H., Mosteller, F., and Vandam, L. D. (1969). *The National Halothane Study*. Bethesda: N.I.H.

Clifton, B. S., and Hotten, W. I. T. (1963). Deaths associated with anaesthesia. *Br. J. Anaesth.*, **35**, 250.

Cogbill, C. L. (1967). Operations in the aged. *Arch. Surg.*, **94**, 202.

Edwards, G., Morton, H. J. V., Pask, E. A., and Wylie, W. D. (1956). Deaths associated with anaesthesia. *Anaesthesia*, **11**, 194.

Feigal, D. W., and Blaisdell, F. W. (1979). The estimation of surgical risk. *Med. Clin. N. Am.*, **63**, 1131.

Hallén, B. (1973). Computerised anaesthetic record keeping. *Acta Anaesthesiol. Scand.* (Suppl.), **52**.

Holland, R. (1970). Special committee investigating deaths under anaesthesia. *Med. J. Austral.*, **1**, 573.

Hovi-Viander, M. (1980). Deaths associated with anaesthesia in Finland. *Br. J. Anaesth.*, **52**, 483.

Lunn, J. N., and Mushin, W. W. (1981). Confidential enquiries into anaesthetic deaths, (in press).

Marx, G. F., Mateo, C. V., and Orkin, L. R. (1973). Computer analysis of postanesthetic deaths. *Anesthesiology*, **39**, 54.

O.P.C.S. (1978). *Mortality Statistics 1975.* D.H.1. no. 2. London: HMSO.

Putnam, L., Jenicek, J. A., Allen, C. R., and Wilson, R. D. (1974). Anaesthesia in the morbidly obese patient. *South. Med. J.*, **67**, 1411.

Rashad, K. F., Goldman, E. J., Graff, T. D., Benson, D. W., and Kelley, E. B. (1965). Baltimore anesthesia study committee: factors in geriatric mortality. *Anesth. Analg. (Cleve.)*, **44**, 462.

Saklad, M. (1941). Grading of patients for surgical procedures. *Anesthesiology*, **2**, 281.

Scott, D. L. (1961). Anaesthetic experiences in 130 major geriatric operations. *Br. J. Anaesth.*, **33**, 354.

Vacanti, C. J., Van Houten, R. J., and Hill, R. C. (1970). A statistical analysis of the relationship of physical status to postoperative mortality in 68 388 cases. *Anesth. Analg. (Cleve.)*, **49**, 564.

Vandam, L. D. (1965). The unfavourable effects of prolonged anaesthesia. *Can. Anaesth. Soc. J.*, **12**, 107.

## EPIDEMIOLOGIE EN ANESTHESIE
## II: FACTEURS INFLUENCANT LA MORTALITE HOSPITALIERE

### RESUME

On a étudé la mortalité à l'hôpital après 108 878 anesthésies adminstrées à Cardiff entre 1972 et 1977. Cela représentait un total de 2391 morts, ce qui correspond à une fréquence brute de mortalité de 2,2 pour 100 des cas. Des données sont exposées sur plusieurs variables importantes qui influencent la mortalité. Celles-ci comprennent l'âge, le sexe, l'évaluation clinque peropératoire, l'etat pré-opératoire, l'organe concerné, le type de l'intervention, le caractère règlé ou urgent de la chirurgie et la durée de l'anesthésie.

## EPIDEMIOLOGIE IN DER ANÄSTHESIE II: FAKTOREN, DIE DIE STERBLICHKEIT IM KRANKENHAUS BETREFFEN

### ZUSAMMENFASSUNG

Die Sterblichkeit im Krankenhaus nach 108 878 Narkosen in Cardiff zwischen 1972 und 1977 wurde untersucht. Die 2391 Gesamtsterbefälle ergaben eine grobe Sterblichkeitsrate von 2,2 pro 100 Fälle. Daten werden über mehrere wichtige Variablen, die die Sterblichkeit beeinflussen, veröffentlicht. Diese schließen Alter, Geschlecht, präoperativen Risiko-score, präoperatives Leiden, Lage der Operation, Operation, sowie Dauer der Narkose und Information, ob es ein Wahl- oder Noteingriff war, mit ein.

## LA EPIDEMOLOGIA EN LA ANESTESIA II – FACTORES QUE AFECTAN AL INDICE DE MORTALIDAD EN HOSPITALES

### SUMARIO

Se ha analizado el índice de mortalidad en hospitales a raiz de las 108.878 anestesías practicadas en Cardiff entre 1972 y 1977. Hubo un total de 2.391 muertes, lo que presenta un índice bruto de mortalidad del 2,2 por cada 100 pacientes. Se presentan datos relativos a diversas variables de importancia que influyen en el índice de mortalidad. Estos incluyen la edad, el sexo, la evaluación clínica previa a la operación, la condición previa a la operación, la propia intervención quirúrjica, si fue electiva o de urgencia, así como la duración de la anestesia.

*Br. J. Anaesth.* (1982), 54, 819

# EPIDEMIOLOGY IN ANAESTHESIA

## III: MORTALITY RISK IN PATIENTS WITH COEXISTING PHYSICAL DISEASE

F. G. R. FOWKES, J. N. LUNN, S. C. FARROW, I. B. ROBERTSON
AND P. SAMUEL

### SUMMARY

The Cardiff Anaesthetic Record System has been used to examine the hospital mortality rates and relative risks for patients having anaesthesia who have certain preoperative conditions coexisting with their disease requiring surgery. Each preoperative condition was associated with a higher mortality rate than occurred in patients with no preoperative condition (for example ischaemic heart disease 7%, diabetes 5.7%, no preoperative condition 0.5%). Mortality was greater for emergency than for elective operations. In contrast to an increasing mortality by age, the relative mortality risk decreased, suggesting that in older age groups coexisting disease may be less important than other risk factors in determining mortality.

Surgical mortality varies not only with the patient's diagnosis and the specific operation performed, but also with other factors which are associated with high risk (Goldstein and Keats, 1970; Feigal and Blaisdell, 1979). Emergency operations tend to be more hazardous than elective procedures (Cogbill, 1967; Vacanti, Van Houten and Hill, 1970). Mortality is often higher in males than females and increases with old age and poor physical status (Beecher and Todd, 1954; Clifton and Hotten, 1963; Bunker et al., 1969). Patients with an acute or chronic disease in addition to the condition requiring surgery are more likely to die overall than those with no concomitant disease (Cogbill, 1967). There is probably an increased mortality in patients with some specific diseases or conditions known to be present before operation (Scott, 1961; Hallén, 1973), but the risk is not well documented. In this paper we examine the mortality associated with certain preoperative conditions which occurred relatively frequently in more than 2300 patients who died during a hospital admission when surgery was performed. Only the risk of dying is considered; cause of death is not described and no attempt has been made to attribute death to anaesthesia, the surgical procedure or the patient's disease.

### METHODS

Since 1958 detailed information has been collected on every inpatient having an anaesthetic in the major hospitals in Cardiff. The data on each patient are recorded on a standard form and are subsequently computerized. Details of the system have been described elsewhere by Mushin and colleagues (1954) and in an accompanying paper (Lunn et al., 1982).

Most of the data are collected by the anaesthetist before the patient undergoes surgery, and include information on the age, sex and physical condition of the patient. The physical condition is recorded in two ways. First, a general clinical assessment is made and the patient allotted to one of five categories: good, minor impairment; major impairment; bad; moribund. This is a subjective assessment by the anaesthetist of the patient's operative risk, the physical condition of the patient playing a major part in determining the risk. In the second method of recording physical condition, the anaesthetist examines a list of 96 specific pre-anaesthetic conditions and notes those that are present in the patient. The conditions are listed by diagnosis (for example ischaemic heart disease, diabetes) and by symptoms and signs (such as atrial fibrillation, dehydration).

Death of the patient either during the operation or after the operation during the same hospital admission is also noted on the anaesthetic recording form. Deaths are identified by the coding clerks who review all deaths occurring in the hospitals and

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ascertain whether each patient had an operation during that admission.

In this study we have analysed data on all 108 878 anaesthetics administered from 1972 to 1977. There were 2391 operative and postoperative deaths during this period. Various factors affecting this mortality in hospital have been described in an accompanying report (Farrow et al., 1982). In this paper the risk of death is analysed for certain physical conditions present before operation. Some patients had several conditions, but each was treated as if it alone was associated with the death; no allowance has been made for interaction between more than one condition in the same patient.

## RESULTS

In analysing the association between the occurrence of specific preoperative conditions and surgical mortality, the conditions chosen were those which occurred relatively frequently in patients who died. Table I shows the prevalence of these conditions amongst the surgical deaths. Ischaemic heart disease and chronic lower respiratory tract infection were the most common specific conditions; less than 10% of patients who died had no recorded preoperative condition. In more than a quarter of patients, the anaesthetist considered that the general health of the patient was impaired by the disease for which the patient was receiving an operation.

TABLE I. *Prevalence of preoperative conditions in surgical deaths*

| Condition | Deaths ($n = 2391 = 100\%$) No. | % |
|---|---|---|
| Impairment of general health by surgical diagnosis | 632 | 26.4 |
| Ischaemic heart disease | 620 | 25.9 |
| Chronic lower respiratory tract infection | 441 | 18.4 |
| Cardiac failure | 182 | 7.6 |
| Obesity | 116 | 4.9 |
| Impaired renal function | 85 | 3.6 |
| Diabetes | 83 | 3.5 |
| No preoperative condition | 206 | 8.6 |

The overall mortality rate for patients with the preoperative conditions listed varied between 2.1% for obesity (2.1 deaths per 100 obese patients having any operation) to 15.8% for cardiac failure (table II). The mortality rate did vary, however, depending on whether the operation was elective or an emergency. For each preoperative condition the mortality was between two and five times higher for emergency than for elective operations. In patients with no preoperative conditions, the overall mortality rate was 0.5%, whilst the rate for emergency operations (1%) was 2.5 times greater than for elective operations (0.4%).

In table II, the relative mortality risk for each condition has been calculated. The relative mortality risk is an estimate of the increased mortality associated with the condition and is the ratio of the mortality rate with the specific preoperative condition to the mortality rate with no such condition. For both emergency and elective operations the relative mortality risk was considerable for each condition. For example, a patient with ischaemic heart disease was 18 times more likely to die from an emergency operation than a patient with no preoperative condition. The increased risk was greater in emergency than elective operations for each condition although the observed differences were not statistically significant (test for heterogeneity of

TABLE II. *Mortality rates and relative risks for preoperative conditions in emergency and elective operations. *Relative mortality risk = (Mortality rate with specific preoperative condition)/(Mortality rate with no pre-operative condition)*

| Condition | Mortality rate (%) All ops | Emergency | Elective | Relative mortality risk* Emergency | Elective |
|---|---|---|---|---|---|
| Impairment of general health by surgical diagnosis | 5.9 | 10.6 | 4.2 | 10.6 | 10.5 |
| Ischaemic heart disease | 7.0 | 18.0 | 4.7 | 18.0 | 11.8 |
| Chronic lower respiratory tract infection | 5.1 | 13.2 | 3.4 | 13.2 | 8.5 |
| Cardiac failure | 15.8 | 31.1 | 10.0 | 31.1 | 25.0 |
| Obesity | 2.1 | 6.6 | 1.3 | 6.6 | 3.3 |
| Impaired renal function | 10.8 | 23.0 | 6.1 | 23.0 | 15.3 |
| Diabetes | 5.7 | 12.7 | 4.3 | 12.7 | 10.8 |
| No preoperative condition | 0.5 | 1.0 | 0.4 | — | — |

relative risks) (Woolf, 1955) for certain individual conditions such as diabetes and impairment of general health by surgical diagnosis.

As operative mortality rates for patients with specific preoperative conditions might have been influenced by the age of the patient, separate mortality rates were calculated for patients aged 0–44 yr, 45–64 yr, and 65 yr and over. Figure 1 shows the mortality rates for certain preoperative conditions by the age of the patient. For each condition, the mortality rate increases with age in both emergency and elective operations, and the increased rate in emergency operations compared with electives is independent of age. In patients with the other preoperative conditions (table I) the pattern of mortality for elective and emergency operations by age was the same as for those shown in figure 1 with one exception: patients with cardiac failure having emergency operations had a 36% mortality at age 45–65 yr and a lower mortality (30%) for those aged 65 yr and more. The age gradient varied for each condition although, in general, the mortality rate in old patients was rarely more than twice that in middle-aged patients. The pattern of mortality for patients with no preoperative condition was similar (fig. 1) and ranged from 0.1% for patients aged 0–44 yr having an elective operation to 9.4% for those aged 65 yr and more having an emergency operation.

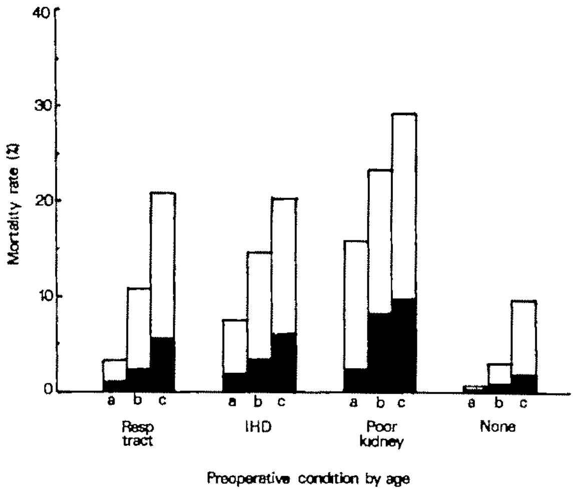

FIG. 1. Mortality rates for selected preoperative conditions in emergency (□) and elective (■) operations by age of patient (a = 0–44 yr; b = 45–64 yr; c = 65 + yr). Resp. tract = Chronic lower respiratory tract infection; IHD = ischaemic heart disease; poor kidney = impaired renal function; none = no preoperative condition.

The relative mortality risk was analysed by age. With few exceptions the pattern of risk was the same for each condition and is shown for ischaemic heart disease and chronic lower respiratory tract infection in figure 2. In contrast to mortality rates which

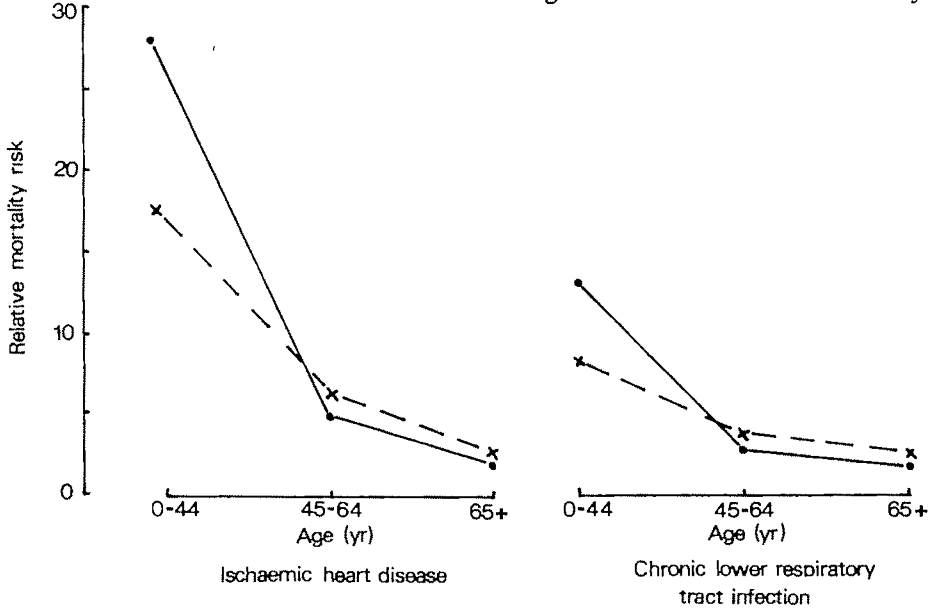

FIG. 2. Relative mortality risk for selected preoperative conditions in emergency (——) and elective (- - -) operations by age of patient. Relative mortality risk = (Mortality rate with specific preoperative condition)/(Mortality rate with no preoperative condition).

increased with age, the relative mortality risk decreased with age, the gradient of decrease being more substantial between ages 0–44 yr and 45–64 yr than from 45–64 yr to 65 yr and more. At ages 0–44 yr, the relative risk was greater in emergency operations, whereas in the older age groups the relative risk was slightly greater in elective operations. For most conditions the relative risk of an operation, whether elective or emergency, at age 0–44 yr was greater than an elective or emergency operation in the older aged groups. For example, the relative risk for a patient aged 0–44 yr with ischaemic heart disease having an emergency operation (28:1) or an elective operation (17:1) was greater than the risk for a patient aged 45–64 yr having an emergency operation (5:1) or an elective operation (6:1).

Some of the variation in mortality rates by age and by elective or emergency operation was undoubtedly a result of the different types of operation performed. In our sample the numbers were too small to analyse reliably mortality for individual operations, but we were able to examine mortality by severity of operation using an established classification (North East Thames Regional Health Authority, 1976) which categorizes operations as major, intermediate and minor. Mortality rates were calculated separately for minor and major operations; intermediate operations were omitted because of some doubt as to the validity of the classification system in separating some intermediate operations from minor or major operations. Table III shows the mortality rates for major and minor elective and emergency operations. For elective operations, each preoperative condition had a higher mortality rate for major operations, although only marginally so for some conditions. Patients with no preoperative condition having an elective operation had a slightly lower mortality rate for major than minor operations, but this difference was not statistically significant ($\chi^2$ test). There was an increased mortality risk for both major and minor elective operations for patients with any preoperative condition compared with those with no such condition. The relative risk was greater for major than minor operations. For emergency major and minor operations, the mortality rates were higher than the corresponding elective operations. Major operations had a higher mortality than minor operations (with the exception of ischaemic heart disease and diabetes), but the number of minor emergency operations performed on patients with each condition were too small to reach a reliable conclusion on the magnitude of the risk for each condition.

Table IV shows the mortality rates for each preoperative condition by the overall clinical assessment allotted to patients by anaesthetists before the operation. In making these assessments the anaesthetists would have considered the presence of specific preoperative conditions, and so the two variables of preoperative condition and overall clinical assessment are not independent. Apart from some disparity in the differences between the "good" and "minor impairment" assessments, the mortality rate for each condition increased the worse the assessment. This could have been because of an increasing severity of preoperative condition or the presence of other conditions or circumstances (such as type of operation) contributing to a worse overall clinical assessment. The mortality of patients with

TABLE III. *Mortality rates for preoperative conditions in minor and major elective and emergency operations. *Mortality in this group based on small numbers for each condition*

| | Mortality rate (%) | | | |
|---|---|---|---|---|
| | Elective | | Emergency | |
| Condition | Minor | Major | Minor | Major |
| Impairment of general health by surgical diagnosis | 3.8 | 4.1 | 9.7 | 10.7 |
| Ischaemic heart disease | 4.6 | 4.8 | 18.5 | 17.2 |
| Chronic lower respiratory tract infection | 2.1 | 3.4 | 6.9 | 13.7 |
| Cardiac failure | 7.1 | 10.2 | 7.7 | 31.7 |
| Obesity | 1.0 | 1.3 | 6.1 | 6.5 |
| Impaired renal function | 2.8 | 6.0 | 13.3 | 24.6 |
| Diabetes | 2.0 | 4.4 | 20.01 | 11.2 |
| No preoperative condition | 0.5 | 0.4 | 0.0 | 1.0 |

TABLE IV. *Mortality rate for preoperative conditions in elective operations by overall clinical assessment. *Mortality in this group based on small numbers for each condition*

| Condition | Good | Minor impairment | Major impairment | Bad | Moribund* |
|---|---|---|---|---|---|
| Impairment of general health by surgical diagnosis | 1.9 | 1.4 | 4.9 | 21.5 | 52.6 |
| Ischaemic heart disease | 1.1 | 1.6 | 4.3 | 20.1 | 56.3 |
| Chronic lower respiratory tract infection | 2.0 | 0.9 | 3.7 | 19.8 | 66.7 |
| Cardiac failure | 5.3 | 4.1 | 7.5 | 20.8 | 28.6 |
| Obesity | 0.3 | 0.3 | 2.2 | 14.6 | 50.0 |
| Impaired renal function | 1.4 | 2.8 | 4.4 | 22.5 | 50.0 |
| Diabetes | 1.3 | 1.6 | 5.8 | 14.9 | — |
| No preoperative condition | 0.2 | 0.7 | 3.5 | 16.1 | 50.0 |

no preoperative condition also varied according to the clinical assessment. For patients with the better clinical assessments, individual preoperative conditions compared with other risk factors may have contributed more to the mortality than for patients with the worse assessments, since the relative mortality risks for specific conditions with assessments of "good" and "minor impairment" were greater than for other assessments. For example, the relative mortality risk of ischaemic heart disease with overall assessment "good" was 1.1/0.2 = 5.5 and with "major impairment" was 4.3/3.5 = 1.2. This pattern of mortality and relative risk was similar for emergency operations; mortality rates were higher than for the corresponding elective mortality rates.

## DISCUSSION

Emergency operations have been shown in other studies (Cogbill, 1967; Vacanti, Van Houten and Hill, 1970) to have a higher overall mortality than elective operations. For each of the preoperative conditions examined in this paper, the mortality rate was, as might be expected, higher for emergency operations (table II). The relative mortality risk was also greater for emergency operations, suggesting that in emergencies, the presence of a preoperative condition makes a greater contribution to mortality than in elective operations. The differences shown could possibly be a result of variation in surgical diagnosis and types of operations performed, but another plausible explanation is that, in the emergency situation, patients with certain complicated conditions before operation are not adequately controlled before surgery. Also, in emergencies occurring outside normal working hours, less experienced junior staff are likely to be involved in more complex cases than during normal elective theatre lists.

In contrast to the increasing mortality rate with age, the relative mortality risk decreased with age for each preoperative condition (fig. 2) suggesting that in older age groups the presence of a preoperative condition was much less important compared with other risk factors in determining mortality. Variations in type of operation performed may partly account for these findings, but the differences could well be related to a greater severity of preoperative condition in younger age groups. At older ages the conditions might be more stable with physiological compensation well established, so that management of the patient during and after the operation is less hazardous. For each condition, the relative mortality risk at age 0–44 yr was greater in emergency operations in contrast to a slightly greater risk in elective operations at older ages. This increased risk in emergency operations in the younger age group might well be a result of the differences mentioned above.

The preoperative condition most frequently studied in terms of its mortality risk is ischaemic heart disease. In a review (Nachlas, Abrams and Goldberg, 1961) of the series published up to 1960, an estimate was made of the overall surgical mortality rate for patients with ischaemic heart disease at just over 6%, which is similar to the 7% mortality found in this study. Comparison between series is difficult because of varying definitions of ischaemic heart disease and "surgical" mortality and differences in the selection of patients. However, ischaemic heart disease does not appear in most series to be associated with greater surgical mortality, the risk being greater if a myocardial infarction has occurred within 3 months before surgery (Arkins, Smessaert and Hicks, 1964). Uncontrolled cardiac failure carries a particularly high risk (16% in this study) and in a series of patients older than 70 years of age was associated with a 30% mortality (Scott, 1961). In examining the risk of developing postoperative cardiac complications, Goldman and others (1977) found that a preoperative third heart sound or jugular venous distension was the most significant risk factor which correlated with life-threatening and fatal cardiac complications.

The mortality risk of other preoperative conditions has been less extensively studied. Deaths in hospital of patients older than 70 years of age having an operation were examined for the period 1952–59 (Scott, 1961). For patients with no preoperative complication, the mortality rate was 6.5%, but for other patients it was 20.2% (obesity), 11.4% (diabetes), 20.0% (bronchitis) and 16.8% (emphysema). These mortality rates are higher than in our series for patients aged 65 yr and more (obesity 5.1%, diabetes 8.5%, and chronic lower respiratory tract infection 8.3%); the differences in magnitude of risk between the two series might be a result of such factors as variation in the selection of patients and the diagnostic criteria used, but might also result from advances in anaesthesia and surgery causing a reduction in risk from the 1950s to 1970s.

The results of this study show that, when considering surgery overall, patients who have certain preoperative conditions are at a greater risk of dying than those who do not. Although we examined more than 100 000 operations, the numbers were still too small to allow analysis of the risk of the preoperative conditions for specific operations or even separately for males and females. Some of the differences in mortality between patients who had a preoperative condition and those who did not might conceivably have resulted from variations in operations performed, although this was controlled to a limited extent by considering emergency and elective operations, and major and minor operations. The relative mortality rates give some idea of the increased risk associated with each condition, and how this varies with some of the parameters shown. However, to aid the anaesthetist and surgeon in making decisions on whether to operate or not, more detailed information is required on the risk from preoperative conditions associated with specific operations (elective and emergencies) and how that risk varies with the patient's age, sex and general physical status.

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## REFERENCES

Arkins, R., Smessaert, A. A., and Hicks, R. G. (1964). Mortality and morbidity in surgical patients with coronary artery disease. *J.A.M.A.*, **190**, 485.

Beecher, H. K., and Todd, D. P. (1954). A study of the deaths associated with anesthesia and surgery. *Ann. Surg.*, **140**, 2.

Bunker, J. P., Forrest, W. H., Mosteller, F., and Vandam, L. D. (eds) (1969). *The National Halothane Study.* Bethesda, Md: National Institutes of Health, National Institute of General Medical Sciences.

Clifton, B. S., and Hotten, W. I. T. (1963). Deaths associated with anaesthesia. *Br. J. Anaesth.*, **35**, 250.

Cogbill, C. L. (1967). Operations in the aged. Mortality related to concurrent disease, duration of anesthesia, and elective or emergency operation. *Arch. Surg.*, **94**, 202.

Farrow, S. C., Fowkes, F. G. R., Lunn, J. N., Robertson, I. B., and Samuel, P. (1982). Epidemiology in anaesthesia. II: Factors affecting mortality in hospital. *Br. J. Anaesth.*, **54**, 000.

Feigal, D. W., and Blaisdell, F. W. (1979). The estimation of surgical risk. *Med. Clin. N. Am.*, **63**, 1131.

Goldman, L., Caldera, D. L., Nussbaum, S. R., Southwick, F. S., Krogstad, D., Murray, B., Burke, D. S., O'Malley, T. A., Goroll, A. H., Caplan, C. H., Nolan, J., Carabello, B., and Slater, E. E. (1977). Multi-factorial index of cardiac risk in noncardiac surgical procedures. *N. Engl. J. Med.*, **297**, 845.

Goldstein, A. jr, and Keats, A. S. (1970). The risk of anesthesia. *Anesthesiology*, **33**, 130.

Hallén, B. (1973). Computerized anaesthetic record-keeping. A clinical study of the preanaesthetic data, the risk of groups and the choice of anaesthetic method. *Acta Anaesthesiol. Scand.* (Suppl. 52), 46.

Lunn, J. N., Farrow, S. C., Fowkes, F. G. R., Robertson, I. B., and Samuel, P. (1982). Epidemiology in anaesthesia. I: Anaesthetic practice over 20 years. *Br. J. Anaesth.*, **54**, 000.

Mushin, W. W., Rendell-Baker, L., Lewis Faning, E., and Morgan, J. H. (1954). The Cardiff Anaesthetic Record System. *Br. J. Anaesth.*, **26**, 298.

Nachlas, M. M., Abrams, S. J., and Goldberg, M. M. (1961). The influence of arteriosclerotic heart disease in surgical risk. *Am. J. Surg.*, **101**, 447.

North East Thames Regional Health Authority (1976). *Major, Intermediate and Minor Operations*, London: Regional Statistical Office.

Scott, D. L. (1961). Anaesthetic experiences in 1300 major geriatric operations. *Br. J. Anaesth.*, **33**, 354.

Vacanti, C. J., Van Houten, R. J., and Hill, R. C. (1970). A statistical analysis of the relationship of physical status to postoperative mortality in 68 388 cases. *Anesth. Analg. (Cleve.)*, **49**, 564.

Woolf, B. (1955). On estimating the relation between blood group and disease. *Ann. Hum. Genet.*, **19**, 251.

## EPIDEMIOLOGIE EN ANESTHESIE
## III: RISQUE VITAL CHEZ LES PATIENTS AYANT UNE MALADIE ORGANIQUE ASSOCIEE

### RESUME

Le système de fichier anesthésique de Cardiff a été utilisé pour étudier les fréquences de décès à l'hôpital et les risques relatifs que couraient les patients subissant une anesthésie et ayant certains états pathologiques pré-opératoires co-existant avec celui qui nécessitait la chirurgie. Chaque état pathologique préopératoire s'accompagne d'un taux de mortalité plus important que celui des patients sans antécédent (par exemple cardiopathie ischémique 7%, diabète 5,7%, pas d'antécédent 0,5%). La mortalité est plus importante pour la chirurgie d'urgence que pour la chirurgie règlée. En contraste, avec une augmentation de la mortalité avec l'âge, le risque vital relatif diminue, ce qui suggère que dans les groupes d'âge les plus avancés, l'existence de tares associées est moins importante que d'autres facteurs de risque pour aggraver la mortalité.

## EPIDEMIOLOGIE IN DER ANÄSTHESIE
## III: STERBLICHKEITSRISIKO VON PATIENTEN MIT ORGANISCHEN ZWEITERKRANKUNGEN

### ZUSAMMENFASSUNG

Das Cardiff Anaesthetic Record System wurde benutzt, um die Sterblichkeit im Krankenhaus und die relativen Risiken für Patienten zu untersuchen, die sich einer Narkose unterziehen müssen und bestimmte präoperative Leiden aufweisen, die neben der Krankheit, die eine Operation verlangt, bestehen. Jedes präoperative Leiden ging mit einer höheren Sterblichkeitsrate einher als dies bei Patienten ohne präoperative Leiden der Fall war (z.B. ischämische Herzkrankheit 7%, Diabetes 5,7% und keine präoperative Leiden 0,5%). Die Sterblichkeit war höher bei Notoperationen als bei Wahleingriffen. Im Gegensatz zu einer mit dem Alter zunehmenden Sterblichkeit, nahm das relative Sterblichkeitsrisiko ab, was die Vermutung nahe legt, daβ in höheren Altersgruppen eine gleichzeitig bestehende Zweiterkrankung weniger wichtig sein könnte als andere Risikofaktoren, die die Sterblichkeit beeinflussen.

## LA EPIDEMOLOGIA EN LA ANESTESIA
## III–RIESGO DE MORTALIDAD EN PACIENTES CON ENFERMEDAD FISICA COEXISTENTE

### SUMARIO

Se ha usado el Sistema de Registros Anestésicos de Cardiff para examinar los índices de mortalidad en los hospitales y los riesgos relativos concernientes a aquellos pacientes bajo anestesia, los cuales presentan ciertas condiciones preoperativas en coexistencia con la enfermedad que motiva la intervención quirúrjica. Cada una de las condiciones preoperativas vino asociada con un índice de mortalidad más alto que el correspondiente a aquellos pacientes sin condición preoperativa alguna (por ejemplo, enfermedad isquémica del corazón 7%, diabetes 5,7%, sin condición preoperativa 0,5%). El índice de mortalidad fue superior en los casos de urgencia que en los de intervención electiva. En contra posición a un creciente índice de mortalidad por razones de edad, el riesgo relativo de mortalidad disminuyó, lo que sugiere que la enfermedad coexistente en los grupos de edad puede que sea menos importante que otros factores de riesgo a la hora de determinar el índice de mortalidad.

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# ONSET TIME AND DURATION OF ACTION FOR ATRACURIUM, ORG NC45 AND PANCURONIUM

L. GRAMSTAD, P. LILLEAASEN AND B. MINSAAS

## SUMMARY

Speed of onset, maximum block, duration of action and 10–25% recovery time for atracurium, Org NC45 and pancuronium were determined using equipotent doses: 330 μg kg$^{-1}$, 66 μg kg$^{-1}$ and 75 μg kg$^{-1}$ respectively. Vein-to-muscle and artery-to-muscle onset times were measured by use of simultaneous recordings. Mean speeds of onset to 95% twitch depression were: atracurium 2.7 min, Org NC45 2.8 min and pancuronium 3.6 min. The median value of maximum neuromuscular block exceeded 98.5% for all drugs and the mean durations of action to 25% recovery of control twitch height were: atracurium 27.6 min, Org NC45 21.9 min and pancuronium 45.1 min. The differences were statistically significant. The recovery period from 10% to 25% twitch response was considerably longer for pancuronium than for the other drugs, which did not differ significantly from each other. We were unable to validate the artery-to-muscle technique in the determination of onset time.

The recently developed neuromuscular blocking drugs, atracurium and Org NC45, are reported to have relatively rapid speeds of onset, intermediate durations of action and relatively fast recovery rates (Agoston et al., 1980; Crul and Booij, 1980; Payne and Hughes, 1981). The relative potencies of the two drugs, and that of pancuronium, were determined previously (Gramstad and Lilleaasen, 1982) and used in a comparison of the clinical properties of atracurium and Org NC45 using pancuronium as the reference drug. To explore any differences in the speeds of onset of the neuromuscular blockers, both vein-to-muscle and artery-to-muscle onset times were measured. The maximum degrees of blockade, durations of action, and speeds of recovery from clinical relaxation were determined.

## PATIENTS AND METHODS

Thirty female patients, ASA class I, undergoing gynaecological operations, gave informed consent to the study. Exclusion criteria were: pregnancy, puerperium, concomitant medication for infectious or other diseases, more than 20% deviation from normal weight, age less than 20 or older than 50 yr.

The patients were premedicated with pethidine 75 mg and atropine 0.6 mg i.m. A catheter was inserted to a vein on the back of the left hand and connected to a continuous infusion of a Ringer's acetate solution. Anaesthesia was induced with diazepam 10 mg, fentanyl 0.2 mg followed by thiopentone 100–500 mg till the eyelash reflex had disappeared, and maintained with 50–70% nitrous oxide in oxygen. Additional fentanyl (0–0.3 mg) was given, if necessary, to supplement anaesthesia. The patients were randomly allocated to three groups, each receiving one of the neuromuscular blocking agents: atracurium, Org NC45 or pancuronium, given in equipotent doses as bolus injections. By extrapolation of the dose–response curves obtained in a previous study (Gramstad and Lilleaasen, 1982), we determined appropriate equipotent doses to be: pancuronium 75 μg kg$^{-1}$, atracurium 330 μg kg$^{-1}$ and Org NC45 66 μg kg$^{-1}$.

The ulnar nerve on both hands was stimulated simultaneously at both wrists via subcutaneous needle electrodes connected to Myotest stimulators delivering supramaximal impulses at 0.1 Hz. The evoked adduction force of each thumb was measured by Statham UC3 transducers connected to a Hewlett–Packard 7702B two-channel recorder, equipped with 8805C amplifiers. The sensitivity of the recording system was adjusted to give reliable measurements to 98.5% twitch depression. Resting thumb tensions were maintained between 200 and 300 g during the recordings.

When the evoked twitch responses on both hands were stable, an arm cuff on the right arm was inflated to more than 200 mm Hg, and the neuromuscular blocking agent was injected over the

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course of 4–5 s via the cannula in the left hand and flushed by a fast-running infusion. Exactly 1 min after the injection, the arm cuff on the right arm was released. Onset of action was recorded on both hands until the first reduction in twitch height was observed (latent onset time) and to 95% depression of twitch height.

Artery-to-muscle onset time is described as the interval from release of the arm cuff until onset of action on the right hand (Minsaas and Stovner, 1980). Vein-to-muscle onset time was recorded on the left hand as the period from the end of the injection until the onset of action. At maximum block a tracheal tube was inserted, and intermittent positive pressure ventilation was maintained in a semi-closed circle absorber system.

On the left hand, which was without any arterial occlusion, the maximum twitch depression was measured, and the duration of action was recorded as the time from injection till 25% recovery of control twitch height. The recovery period from clinical to subclinical level of neuromuscular blockades was measured as the time interval from 10% to 25% twitch response.

Student's *t* test was used for statistical analysis.

## RESULTS

Table I shows that the three groups of patients were similar in age, weight and body surface area.

No major differences were seen between the drugs or between the two methods used to assess the speed of onset (table II). The mean latent onset times were about 50 s, except the artery-to-muscle onset time for pancuronium, which was 39 s. The vein-to-muscle onset times to 95% twitch depression were shorter for atracurium and Org NC 45 than for pancuronium. The artery-to-muscle onset time to 95% twitch depression for pancuronium was shorter than those for the other two drugs.

The maximum twitch depression exceeded 98.5% in nine of 10 patients in the atracurium and pancuronium groups, and in all patients receiving Org NC 45.

TABLE I. *Selected characteristics of the patients. Values are mean ± SD*

| Drug group | *n* | Age (yr) | Weight (kg) | Body surface area ($m^2$) |
|---|---|---|---|---|
| Atracurium | 10 | 30.0±3.4 | 58.5±2.9 | 1.65±0.06 |
| Org NC 45 | 10 | 34.2±5.6 | 62.1±5.5 | 1.69±0.08 |
| Pancuronium | 10 | 31.9±3.8 | 58.2±5.7 | 1.62±0.09 |

TABLE II. *Onset time (mean ± SEM) for the three drugs measured simultaneously using the two techniques. *$P < 0.05$ compared with atracurium and Org NC 45. **$P < 0.01$ compared with vein-to-muscle onset time (paired t test)*

| Drug | Latent onset time (s) | Onset time to 95% block (s) |
|---|---|---|
| Vein-to-muscle | | |
| Atracurium | 47±2.1 | 161±10.3 (*n* = 9) |
| Org NC 45 | 51±2.8 | 168±9.2 |
| Pancuronium | 45±1.7 | 215±24.0 |
| Artery-to-muscle | | |
| Atracurium | 51±3.5 | 224±21.1 (*n* = 9)** |
| Org NC 45 | 51±4.3 | 201±23.4 |
| Pancuronium | 39±2.8* | 181±23.1 (*n* = 8) |

The duration of action for pancuronium was considerably longer than for the two other drugs, the mean value being slightly more than twice that for Org NC 45, and nearly twice that for atracurium. The differences were significant for all three drugs (table III).

The recovery of twitch response from 10% to 25% was 2 and 2.5 times faster for atracurium and Org NC 45, respectively, than for pancuronium (table III).

## DISCUSSION

No significant differences in vein-to-muscle onset times were seen between the drugs. Although the latent artery-to-muscle onset time was shorter for pancuronium than for atracurium and Org NC 45, no significant differences were seen to 95% twitch depression. Vein-to-muscle onset time to 95% block is of clinical importance, because intubation is easily performed at this degree of blockade, as reported by Ali and Savarese (1980), using tubocurarine. Estimated intubating times with our doses should therefore be 2.7 min for atracurium, 2.8 min for Org NC 45, and 3.6 min for pancuronium. Payne and Hughes (1981) observed relaxed vocal cords and easy endotracheal intubation within 2 min of the

TABLE III. *Duration of action (mean ± SEM) to 25% recovery of control twitch height, and time course from 10% to 25% recovery. **$P < 0.01$ compared with atracurium. ***$P < 0.001$ compared with atracurium and Org NC 45*

| Drug | Duration of action (min) | Recovery time 10–25% (min) |
|---|---|---|
| Atracurium | 27.6±1.4 | 4.8±0.3 |
| Org NC 45 | 21.9±1.4** | 3.8±0.4 |
| Pancuronium | 45.1±4.2*** | 9.6±1.0*** |

injection of atracurium 0.3 mg kg$^{-1}$. Krieg and colleagues (1980) found good to excellent conditions when intubation was performed 2 min after the injection of Org NC 45 72 µg kg$^{-1}$. Comparisons with previous reports on onset times for pancuronium are often inapplicable because of large variations in dose, frequency of nerve stimulation and definition of onset time. However, Crul and Booij (1980), in their comparative study, observed a significantly longer onset time to maximum effect for pancuronium than for Org NC 45. In our study, we chose not to determine the time course to maximum effect, as this measurement is influenced by increasing the sensitivity of the recordings, if twitch response approximates 0.

The similarity between latent vein-to-muscle and artery-to-muscle onset times for the drugs is noteworthy, because vein-to-artery circulation time is reported to be about 10–15 s (David, Saito and Heyman, 1961). The purpose of measuring the artery-to-muscle onset time is to exclude this variable parameter. The similar latent onset times can be explained by a decrease in the concentration of free drug in blood during the 1st minute after injection. By also having a prolonged onset time to 95% block after 1 min delay in blood, this should be most apparent for atracurium and Org NC 45. These observations indicate that artery-to-muscle onset time is inadequate for determining the speed of onset of neuromuscular blockers.

Median twitch depression exceeded 98.5% for all three drugs. From cumulative dose–response determinations (Gramstad and Lilleaasen, 1982) on a similar patient population, the present doses would be expected to produce a mean response of 98.1%. This may indicate that the dose–response curves are shifted to the left for all three drugs, when these are given in one bolus injection.

Duration of action for atracurium and Org NC 45 was about half that for pancuronium, and Org NC 45 was significantly shorter-acting than atracurium. Payne and Hughes (1981) showed that atracurium 0.3 mg kg$^{-1}$ provided adequate surgical relaxation for 15–20 min, which is comparable to our results. Duration to 25% recovery of twitch height for Org NC 45 is reported to be 15 min after 43 µg kg$^{-1}$ (Crul and Booij, 1980), 17.8 min after 70 µg kg$^{-1}$ (Agoston et al., 1980) and 19.1 min after 75 µg kg$^{-1}$ (Krieg et al., 1980), slightly shorter than the present findings (21.9 min after 66 µg kg$^{-1}$). Recent reports state that the duration to 25% recovery for pancuronium is 34.4 min after 62 µg kg$^{-1}$ (Krieg, Crul and Booij, 1980) and 32 min after 65 µg kg$^{-1}$ (Crul and Booij, 1980), both comparable to the 45 min after 75 µg kg$^{-1}$ demonstrated in this study. Agoston and colleagues (1980) reported that Org NC 45 appeared to have two-to-three-fold shorter action than pancuronium and this agrees with our results.

Because the abdominal musculature is excellently relaxed at 90% twitch depression, but generally feels "tight" at the 75% level (Ali and Savarese, 1976), the 10% to 25% recovery time is of clinical interest. We found the transition period from clinical to subclinical relaxation to be considerably decreased with atracurium and Org NC 45 compared with pancuronium. This implies that neuromuscular monitoring is a useful guide to further injections of the new drugs, to avoid undue fluctuations in effect and to exploit their dynamic properties to conduct a desired course of muscle relaxation.

In summary, atracurium and Org NC 45 produce neuromuscular block insignificantly faster than pancuronium. Even though Org NC 45 is shorter-acting than atracurium, both drugs have an intermediate duration of action, which is shorter than that of pancuronium.

## ACKNOWLEDGEMENTS

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## REFERENCES

Agoston, S., Salt, P., Newton, D., Bencini, A., Boosma, P., and Erdmann, W. (1980). The neuromuscular blocking action of Org NC 45, a new pancuronium derivative, in anaesthetized patients. A pilot study. *Br. J. Anaesth.*, 52, 53S.

Ali, H.H., and Savarese, J.J. (1976). Monitoring of neuromuscular function. *Anesthesiology*, 45, 216.

——— (1980). Stimulus frequency and dose–response curve to d-tubocurarine in man. *Anesthesiology*, 52, 36.

Crul, J.F., and Booij, L.H.D.J. (1980). First clinical experiences with Org NC 45. *Br. J. Anaesth.*, 52, 49S.

David, N.J., Saito, Y., and Heyman, A. (1961). Arm to retina fluorescein appearance time. *Arch. Neurol.*, 5, 165.

Gramstad, L., and Lilleaasen, P. (1982). Dose–response relation for atracurium, Org NC 45 and pancuronium. *Br. J. Anaesth.*, 54, 647.

Krieg, N., Crul, J.F., and Booij, L.H.D.J. (1980). Relative potency of Org NC 45, pancuronium, alcuronium and tubocurarine in anaesthetized man. *Br. J. Anaesth.*, 52, 783.

—— Mazur, L., Booij, L.H.D.J., and Crul, J.F. (1980). Intubation conditions and reversibility of a new non-depolarizing neuromuscular blocking agent, Org NC 45. *Acta Anaesthesiol. Scand.*, 24, 423.

Minsaas, B., and Stovner, J. (1980). Artery-to-muscle onset time for neuromuscular blocking drugs. *Br. J. Anaesth.*, 52, 403.

Payne, J.P., and Hughes, R. (1981). Evaluation of atracurium in anaesthetized man. *Br. J. Anaesth.*, 53, 45.

## LATENCE DE DEBUT D'ACTION ET DUREE D'ACTION DE L'ATRACURIUM, DE L'ORG NC45 ET DU PANCURONIUM

### RESUME

Les temps de début d'action, de bloc maximum, de durée d'action et de 10 et 25% de récupération ont eté déterminés pour l'atracurium, l'Org NC45 et le pancuronium, en utilisant des doses équipotentes: respectivement $330\,\mu g\,kg^{-1}$; $66\,\mu g\,kg^{-1}$ et $75\,\mu g\,kg^{-1}$. Les temps de passage veine à muscle ont été mesurés par des enregistrements simultanés. Les vitesses moyennes d'obtention d'une dépression de 95% du twitch étaient 2,7 min pour l'atracurium, 2,8 min pour l'Org NC45 et 3,6 min pour le pancuronium. La valeur moyenne de bloc neuromusculaire maximum dépassait 98,5% pour tous les agents et les durées moyennes d'action jusqu'à une récupération à 25% de la valeur témoin du twitch était: 27,6 min pour l'atracurium, 21,9 min pour l'Org NC45 et 45,1 min pour le pancuronium. Les différences étaient statistiquement significatives. La période de récupération entre 10 et 25% du twitch était considérablement plus longue avec le pancuronium qu'avec les autres agents, qui ne différaient pas beaucoup entre eux. Nous n'avons pas pû valider la technique artère-muscle dans la détermination du délai d'installation.

## WIRKUNGSEINTRITT UND WIRKUNGSDAUER VON ATRACURIUM, ORG NC45 UND PANCURONIUM

### ZUSAMMENFASSUNG

Die Geschwindigkeit des Wirkungseintritts, das Wirkungsmaximum, die Wirkungsdauer und die 10–25% Erholungszeit für Atracurium, Org NC45 und Pancuronium wurden bestimmt, indem man äquipotente Dosen ($330\,\mu g\,kg^{-1}$, $66\,\mu g\,kg^{-1}$ und $75\,\mu g\,kg^{-1}$) in obiger Reihenfolge verwendete. Der Wirkungseintritt nach i.v. und i.a. Gabe wurde durch parallele Messungen am Muskel bestimmt. Der mittlere Wirkingseintritt der 95%igen Hemmung der Kontraktilität trat im Mittel bei Atracurium nach 2,5 min, bei Org NC45 nach 2,8 min und bei Pancuronium nach 3,6 min ein. Der Mittelwert des maximalen neuromuskulären Blocks lag bei allen Substanzen über 98,5% und die mittlere Wirkungsdauer bis zur Erholung der Kontraktilität auf 25% der Kontrollwerte betrug bei Atracurium 27,6 min, bei Org NC45 21,9 min und bei Pancuronium 45,1 min. Die Unterschiede waren statistisch signifikant. Die Dauer der Erholung von 10% Kontraktilität auf 25% war bei Pancuronium wesentlich länger als bei den anderen Substanzen, zwischen denen kein signifikanter Unterschied bestand. Es war uns nicht möglich, den Wirkungseintritt am Muskel nach i.a. Gabe auszuwerten.

## TIEMPO DE INICIO Y DURACION DE LA ACCION DEL ATRACURIO, ORG NC45 Y DEL PANCURONIO

### SUMARIO

Se determinó la velocidad del inicio, el bloqueo máximo, la duración de la acción y el tiempo de recuperación del 10–25% en cuanto al atracurio, al Org NC45 y al pancuronio usándose dosis equipotentes: $330\,\mu g\,kg^{-1}$, $66\,\mu g\,kg^{-1}$ y $75\,\mu g\,kg^{-1}$, respectivamente. Se midieron los tiempos de inicio vena-músculo y arteria-músculo por medio de registros simultáneos. La velocidad media del inicio para una depresión de contracción del 95% era de: atracurio 2,7 min., Org NC45 2,8 min. y pancuronio 3,6 min. El valor medio del bloqueo neuromuscular máximo sobrepasaba del 98,5% para todas las substancias y las duraciones promedias de la acción en una recuperación del 25% de la altura de contracción de control eran de: atracurio 27,6 min., Org NC45 21,9 min. y pancuronio 45,1 min. Las diferencias eran significantes desde el punto de vista estadístico. El periodo de recuperación de una respuesta de contracción del 10% al 25% fue considerablemente mayor para el pancuronio que para las demás substancias, las que no difirieron mucho una de la otra. No estuvimos en condiciones para validar la técnica arteria-músculo en la determinación del tiempo de inicio.

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# HAEMODYNAMIC EFFECTS OF MIDAZOLAM AND THIOPENTONE DURING INDUCTION OF ANAESTHESIA FOR CORONARY ARTERY SURGERY

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## SUMMARY

The cardiovascular effects of thiopentone 3 mg kg$^{-1}$ and midazolam 0.3 mg kg$^{-1}$ were observed during induction of anaesthesia in 16 premedicated patients about to undergo myocardial revascularization. There were no significant changes in either group in cardiac output or central venous pressure. The heart rate in both groups showed an increase at 3 min and thereafter returned to control values. After 3 min, there was a significant decrease in both arterial pressure and peripheral resistance by 12% and 15% (mean values) respectively from control values in the group receiving midazolam, whereas after thiopentone the peripheral resistance increased by approximately 13% and was not affected by a further dose of thiopentone 1 mg kg$^{-1}$.

Midazolam maleate, a relatively new water-soluble benzodiazepine has been administered i.v. either to produce sedation or to induce anaesthesia (Conner et al., 1978; Fragen, Crahl and Caldwell, 1978; Reeves, Corssen and Halcomb, 1978; Reeves et al., 1979). Reeves, Samuelson and Lewis (1979) studied the haemodynamic effects of this drug during induction of anaesthesia in 10 patients undergoing myocardial revascularization. Since then the drug has been reformulated as the hydrochloride and the study reported here compares the acute haemodynamic effects of thiopentone and midazolam hydrochloride when they were used to induce anaesthesia in patients undergoing coronary artery bypass surgery.

## METHODS

Sixteen patients (14 male, two female) undergoing elective surgery for coronary artery disease consented to the investigation after the nature and purpose of the study had been explained to them. Relevant data are shown in table I. The patients were allocated to each group using a series of random numbers.

The doses of β-blockers required to minimize symptoms and cause resting heart rates around 70 beat min$^{-1}$ vary widely in different patients with coronary disease: 40 mg to more than 500 mg daily for propanolol and 50 mg to more than 400 mg daily for atenolol. In the thiopentone group two patients were receiving propanolol (dose range 80–200 mg) and four received atenolol (dose range 100–200 mg daily). In the midazolam group, four had received atenolol (dose range 100–200 mg daily) and three propanolol (dose range 80–160 mg daily).

All patients received papaveretum 10–20 mg, hyoscine 0.2–0.4 mg and droperidol 5 mg i.m. approximately 60 min before induction of anaesthesia. In none of these patients was the ventricular function sufficiently impaired to justify pulmonary artery catheterization (Lowenstein and Teplick, 1980; Mangano, 1980) and measurements were restricted to those which can be obtained using conventional monitoring: heart rate, arterial pressure, central venous pressure and cardiac output (fig. 1).

When the patients arrived in the induction area a conventional four lead e.c.g. was recorded. I.v., radial artery and superior vena caval (via the right jugular vein) cannulae were introduced under local anaesthesia with 1% lignocaine. Mean and dynamic

TABLE I. *Relevant patient data. Where appropriate, values are mean ±SEM*

| | Thiopentone | Midazolam |
|---|---|---|
| Age (yr) | 55.5±1.88 | 57.2±2.02 |
| Weight (kg) | 75.0±2.77 | 76.0±4.44 |
| Height (cm) | 171.0±2.42 | 172.0±3.27 |
| Sex (M/F) | 8/0 | 6/2 |
| Drugs | | |
| β-Blockers | 6 | 7 |
| Nitrates | 5 | 6 |

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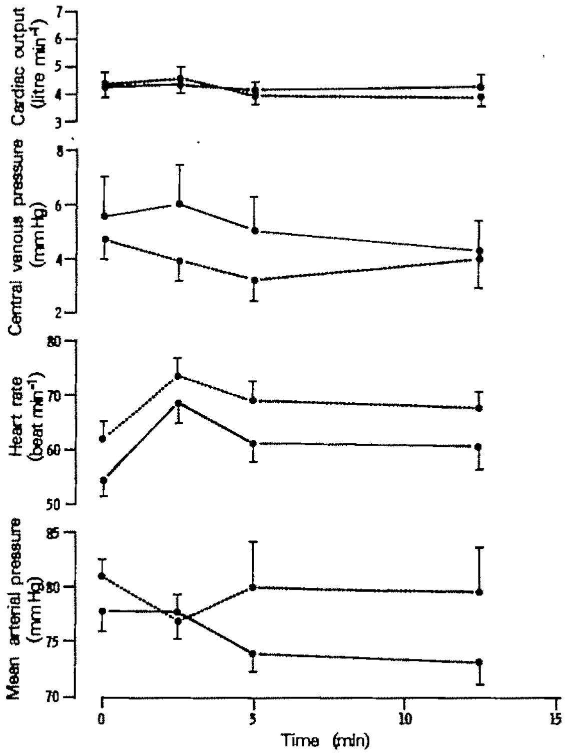

FIG. 1. Values (mean ± SEM) for cardiac output, central venous pressure, heart rate and mean arterial pressure during induction of anaesthesia. 0 = Control after preoxygenation; ●——● = midazolam ($n = 8$); ●---● thiopentone ($n = 8$). Only the following changes were statistically significant: (1) The increase in heart rate 2–3 min after both thiopentone and midazolam ($P < 0.01$); (2) The decrease in mean arterial pressure at 2–3 min after thiopentone ($P < 0.01$) and after midazolam at 5 min ($P < 0.01$) and at 10 min ($P < 0.05$).

arterial and central venous pressures and the e.c.g. were displayed on an oscilloscope or a pen-recorder, and the beat-by-beat heart rate using a digital display.

Cardiac output was measured using dye dilution (indocyanin green, Guilford Instrument Laboratories Model 140). Duplicate readings were taken after preoxygenation before induction of anaesthesia, and thereafter starting at 2, 5 and 10 min after completing the injection of each drug. The coefficient of variation of duplicate readings was 3.5%. Samples of arterial blood were collected anaerobically in heparinized syringes for the measurement of pH, $Pa_{O_2}$ and $Pa_{CO_2}$ (Radiometer ABL 1).

After preoxygenation for 3 min using a Magill breathing system control values for cardiac output were measured and anaesthesia was induced either with midazolam 0.3 mg kg$^{-1}$ or thiopentone 3 mg kg$^{-1}$. Each drug was administered during a period of 30 s. Oxygen 100% was administered throughout each study from a Magill system. Seven of the eight patients who received thiopentone required an additional dose (1 mg kg$^{-1}$), one by 3 min and six between 5 and 10 min in order to complete the study. Once the last cardiac output measurement was made, anaesthesia was continued in a manner appropriate for these patients.

Statistical analysis was performed using analysis of variance and *t* tests where applicable.

## RESULTS

The mean induction time for midazolam was 30 s (range 12–45 s) and for thiopentone 16 s (range 10–30 s). The patients receiving midazolam did not become apnoeic, they tolerated an airway, inflation was not required and they remained asleep throughout the period of measurement.

In contrast, those receiving thiopentone all became apnoeic for a period of 20–45 s. Ventilation of the lungs was assisted using a Magill system until regular satisfactory spontaneous ventilation had returned. One patient started to recover at 3 min and six at 5 min. An additional dose of thiopentone 1 mg kg$^{-1}$ caused no obvious haemodynamic or respiratory effects, and allowed observations to be made for a period comparable to that in the midazolam group.

The haemodynamic data are shown in figures 1 and 2. The following observations can be made.

Neither drug caused any significant change in cardiac output and there were no significant differences between the two groups of patients.

The mean resting heart rate was 7 beats slower in the midazolam group, but this difference was not statistically significant. The pattern of change was the same for both drugs. There was an initial increase in rate, but by 5 min values returned to control and remained so for the duration of the period of observation.

In those receiving thiopentone the mean arterial pressure decreased initially from 83 mm Hg to 74 mm Hg; thereafter it returned to control values. With midazolam the mean pressure did not change immediately, but by 5 min it had decreased from 75 to 68 mm Hg after which it appeared stable and at 10 min the value was 66 mm Hg, a reduction of approximately 12%.

Although the trends observed for central venous pressure appeared to be different for the two drugs (fig. 1), none of the changes observed was statistically significant.

The changes in peripheral vascular resistance are illustrated in figure 2. In the patients receiving midazolam resistance decreased progressively from 17.4 units to 14.9 at 5 min (approximately 15%; $P < 0.05$); thereafter there was little further change. Although there was, in the patients receiving thiopentone, a transient initial decrease in mean peripheral vascular resistance (approximately 11%) which was not statistically different from that obtaining in the midazolam group (fig. 2), resistance subsequently increased to slightly greater than control values and was not affected by the additional dose of thiopentone (1 mg kg$^{-1}$) which was given to seven of the patients during this period (fig. 2). By 5 min, the difference between midazolam and thiopentone has become significant ($P < 0.05$).

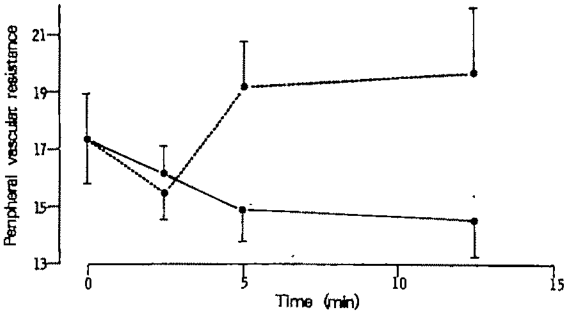

FIG. 2. Changes in peripheral resistance (mean ± SEM) during induction of anaesthesia with midazolam ($n = 8$) ●——● and thiopentone ($n = 8$) ●---●. 0 = Control values after preoxygenation. Peripheral vascular resistance calculated as (mean arterial pressure − mean central venous pressure)/cardiac output, expressed in arbitrary units. By 5 min the differences between the thiopentone and midazolam groups were significant ($P < 0.05$).

The mean heart rate–systolic pressure products (mean ± SEM) for thiopentone were: control 7539 ± 584; at 2.5 min 8359 ± 783; at 5 min 8010 ± 718; at 10 min 7819 ± 974. For midazolam these values were 7312 ± 542, 7584 ± 645, 6327 ± 573 and 6474 ± 772 respectively. None of the changes was statistically significant, either within each group or between groups.

Blood-gas data are shown in table II. The ease of maintaining the airway in the patients receiving midazolam and the absence of apnoea compared with those receiving thiopentone has already received comment. After the administration of the drug $Pa_{CO_2}$ in the group receiving midazolam increased slightly from a mean value of 5.9 kPa to 6.2 kPa. After preoxygenation, none of the changes in $Pa_{CO_2}$, $Pa_{O_2}$ and pH was statistically significant in either group.

## DISCUSSION

The 16 patients in this study were all suffering from symptomatic coronary artery disease and all received either three or four coronary artery vein grafts. In such patients any substantial increase in heart rate or arterial pressure during the period of induction of anaesthesia (increase in the rate – pressure product) is to be avoided (Nelson et al., 1974). The data presented here suggest that the haemodynamic and respiratory effects of midazolam are compatible with this aim since it has relatively minor effects on the circulation. This confirms the view expressed about this drug by Reeves, Samuelson and Lewis (1979) who made haemodynamic observations on 10 similar patients, who were premedicated with morphine sulphate 0.1 mg kg$^{-1}$ and hyoscine 6–8 μg kg$^{-1}$ up to 5 min, compared with 10–15 min in the present study, after the injection of midazolam in a dose of only 0.2 mg kg$^{-1}$. The long and more variable induction time (mean 44 s; range 30–90 s) in their study, compared with the present one (mean 30 s; range 12–45 s), is probably a result of the heavier premedication and the larger dose of midazolam (0.3 mg kg$^{-1}$) reported here.

In the present study there were no significant

TABLE II. *Values (mean ± SEM for arterial pH $Pa_{O_2}$ and $Pa_{CO_2}$ during induction of anaesthesia with either thiopentone* (n = *8) or midazolam* (n = *8)*

| | pH | | $Pa_{O_2}$ (kPa) | | $Pa_{CO_2}$ (kPa) | |
|---|---|---|---|---|---|---|
| Time | Thiopentone | Midazolam | Thiopentone | Midazolam | Thiopentone | Midazolam |
| Pre-induction | | | | | | |
| Before $O_2$ | 7.40 ± 0.01 | 7.38 ± 0 | 10.2 ± 0.29 | 9.4 ± 0.50 | 5.2 ± 0.20 | 5.4 ± 0.16 |
| After $O_2$ | 7.38 ± 0.01 | 7.37 ± 0.01 | 48.0 ± 4.72 | 49.5 ± 3.09 | 5.6 ± 0.13 | 5.7 ± 0.13 |
| 2–3 min | 7.37 ± 0.01 | 7.34 ± 0.01 | 57.4 ± 1.23 | 47.9 ± 3.33 | 5.6 ± 0.32 | 5.9 ± 0.12 |
| 5 min | 7.37 ± 0.01 | 7.34 ± 0.01 | 56.0 ± 2.10 | 51.2 ± 3.03 | 5.7 ± 0.24 | 6.2 ± 0.17 |
| 10–15 min | 7.36 ± 0.01 | 7.34 ± 0.01 | 48.6 ± 6.39 | 48.5 ± 5.34 | 5.7 ± 0.20 | 5.9 ± 0.09 |

changes in cardiac output in patients in whom anaesthesia was induced with either thiopentone or midazolam, confirming the findings of Reeves, Samuelson and Lewis (1979) for midazolam. Following both drugs there was an initial increase in heart rate, seen by 3 min, which then returned to control values.

Differences between thiopentone and midazolam were seen in the changes in mean arterial pressure and systemic vascular resistance. After an initial decrease in both values at 3 min in the patients who received thiopentone, both the mean arterial pressure and the peripheral resistance returned to control values, during the period 5–10 min after injection of the drug. This result was not changed by an additional dose of 1 mg kg$^{-1}$ in seven of the eight patients who required such a dose to maintain hypnosis for 10–15 min. In contrast, in the patients who received midazolam the arterial pressure and peripheral vascular resistance both showed a significant decrease which, after 5 min, continued unchanged for the duration of the study. Changes in the rate–pressure product were not statistically significant in the present study which is in agreement with Reeves, Samuelson and Lewis (1979).

Reeves and his associates (1979) related the tachycardia after the injection of midazolam to an observed increase in $Pa_{CO_2}$ from 5.32 kPa to 6.12 kPa. However, in the present study, although there was a tendency for $Pa_{CO_2}$ to increase in the patients who received midazolam, these changes were much smaller than those observed by Reeves, Samuelson and Lewis (1979) and did not reach statistical significance. Moreover the tachycardia was transient, maximal within 2–3 min and had returned to control values by 5 min when the $Pa_{CO_2}$ was maximal. Also, in artificially ventilated, anaesthetized animals with the blood-gases maintained constant, the onset of action of midazolam is associated with marked tachycardia (Whitwam et al., 1980) and it would be reasonable to assume that this transient increase in heart rate is a result of the haemodynamic effects of the drug, and not secondary to blood-gas changes.

It was concluded that induction of anaesthesia with midazolam in patients with coronary artery disease is accompanied by a relatively stable cardiovascular system with a modest reduction in peripheral vascular resistance. The absence of apnoea in the present study could be regarded as advantageous compared with thiopentone. Such is the smoothness and stability of the induction period with midazolam that it could well become an important agent for the induction of anaesthesia by the i.v. route.

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## REFERENCES

Conner, J. T., Katz, R. L., Pagano, P. R., and Graham, C. W. (1978). RO 21 3981 for intravenous surgical premedication and induction of anesthesia. *Anesth. Analg. (Cleve.)*, 57, 1.

Fragen, R. J., Crahl, F., and Caldwell, N. (1978). A water-soluble benzodiazepine, RO 21 3981, for induction of anesthesia. *Anesthesiology*, 49, 41.

Lowenstein, E., and Teplick, R. (1980). To (PA) catheterise or not to (PA) catheterise—That is the question. *Anesthesiology*, 53, 361.

Mangano, D. T. (1980). Monitoring pulmonary arterial pressure in coronary artery disease. *Anesthesiology*, 53, 364.

Nelson, R. R., Gobel, F. L., Jorgensen, C. R., Wang, K., Wang, Y., and Taylor, J. L. (1974). Haemodynamic predictors of myocardial oxygen consumption during static and dynamic exercise. *Circulation*, 50, 1179.

Reeves, J. G., Corssen, G., and Halcomb, C. (1978). Comparison of two benzodiazepines for anaesthesia induction—midazolam. *Can. Anaesth. Soc. J.*, 25, 211.

——Samuelson, P. N., and Lewis, S. (1979). Midazolam maleate induction in patients with ischaemic heart disease: haemodynamic observations. *Can. Anaesth. Soc. J.*, 26, 402.

——Vinik, R., Hirchfield, A. M., Holcomb, C. M., and Strong, S. (1979). Midazolam compared with thiopentone as a hynotic component in balanced anaesthesia: a randomized, double blind study. *Can. Anaesth. Soc. J.*, 26, 42.

Whitwam, J. G., Scott, W. A. C., Kurimoto, S., Orchard, C., and Chakrabarti, M. K. (1980). Cardiovascular effects of midazolam (RO 21 3981) in the dog. *Br. J. Anaesth.*, 52, 954P.

## EFFETS HEMODYNAMIQUES DU MIDAZOLAM ET DU THIPENTONE PENDANT L'INDUCTION DE L'ANESTHESIE POUR UNE INTERVENTION CHIRURGICALE SUR L'ARTERE CORONAIRE

### RESUME

Les effets cardiovasculaires du thiopentone administré à raison de 3 mg/kg$^{-1}$ et du midazolam administré à raison de 0,3 mg/kg$^{-1}$, ont été observés pendant l'induction de l'anesthésie sur des malades ayant déjà reçu une prémédication en attendant de subir une revascularisation myocardique. Il n'y a eu aucun changement significatif dans le débit cardiaque ou dans la pression veineuse centrale, dans l'un ou l'autre groupe. On a constaté, après trois minutes, dans ces deux groupes, une augmentation de la fréquence cardiaque, mais celle-ci est ensuite retournée aux valeurs témoins. Après trois minutes, il y a eu une baisse importante de la pression artérielle et de la résistance périphérique, respectivement de 12 et de 15% (valeurs moyennes) par rapport aux valeurs témoins, dans le groupe auquel on avait administré du midazolam, alors qu'on a constaté dans le groupe ayant reçu du thiopentone une augmentation d'approximativement 13% de la résistance périphérique et que celle-ci n'a pas eté autrement affectée par une dose supplémentaire de thiopentone de 1 mg/kg$^{-1}$.

## HÄMODYNAMISCHE EFFEKTE VON MIDAZOLAM UND THIOPENTAL WÄHREND DER NARKOSEEINLEITUNG FÜR DIE KORONARARTERIEN-OPERATION

### ZUSAMMENFASSUNG

Die Kreislaufwirkungen von Thiopental i.v. 3 mg $kg^{-1}$ und Midazolam 0,3 mg $kg^{-1}$ wurden während der Narkoseeinleitung bei 60 prämedizierten Patienten beobachtet, die sich einer koronaren Bypass-Operation unterziehen mußten. Es traten in beiden Gruppen keine signifikanten Änderungen des Minutenvolumens und des zentralen Venendruckes auf. Die Herzfrequenz stieg in beiden Gruppen um 3 $min^{-1}$ an und kehrte danach zu den Kontrollwerten zurück. Nach 3 Minuten fiel sowohl der arterielle Druck als auch der periphere Gefäßwiderstand um 12% und 15% (Mittelwert) gegenüber den Kontrollwerten in der Midazolam-Gruppe ab, während nach Thiopental der periphere Gefäßwiderstand um ungefähr 13% zunahm und durch eine weitere Dosis von Thiopental (1 mg $kg^{-1}$) i.v. nicht mehr beeinflußt wurde.

## EFECTOS HEMODINAMICOS DEL MIDAZOLAN Y DE LA TIOPENTONA DURANTE LA INDUCCION DE ANESTESIA TENDENTE A INTERVENCION QUIRURJICA DE LA ARTERIA CORONARIA

### SUMARIO

Se observaron los efectos cardiovasculares de 3 mg $kg^{-1}$ de tiopentona y de 0,3 mg $kg^{-1}$ de midazolan durante la inducción de anesthesia en 16 pacientes premedicados que iban a ser sometidos a una revascularización miocardial. No hubo cambio significativo alguno en la producción cardiaca ni en la presión venosa central de ninguno de los dos grupos. El ritmo cardiaco de ambos grupos mostró un incremento a los 3 minutos y, posteriormente, volvió a los valores de control. Hubo una disminución significativa después de trancurridos 3 minutos, tanto en la presión arterial como en la resistencia periférica, del 12% y del 15% (valores medios) respectivamente con respecto a los valores de control del grupo sometido a midazolan, mientras que después de la tiopentona la resistencia periférica aumentó en el 13% aproximadamente y no quedó afectada por una dosis complementaria de de 1 mg $kg^{-1}$ de tiopentona.

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# EFFECT OF EXTRADURAL ANALGESIA USING BUPIVACAINE AND 2-CHLOROPROCAINE ON INTERVILLOUS BLOOD FLOW DURING NORMAL LABOUR

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## SUMMARY

The effect of lumbar extradural analgesia on intervillous blood flow (IBF) during labour was studied in 26 healthy parturients using an i.v. bolus injection of xenon-133. There was a 19% decrease (n.s.) in mean IBF in six parturients (non-extradural control group). Mean IBF increased by 37.5% when 0.25% bupivacaine 10 ml was used and by 35.2% when 2% 2-chloroprocaine 10 ml was used (n.s.). When the two extradural groups were combined, the mean difference between $IBF_1$ and $IBF_2$ was $45 \pm 112$ ml min$^{-1}$ dl$^{-1}$. This increase is statistically significant ($P < 0.05$). The improvement in IBF after extradural block was considered to be a result of the decreased uterine vascular resistance, as no significant changes were observed in arterial pressure, uterine activity or uterine tone.

Sufficient placental blood flow during labour is of primary importance for the well-being of the fetus. Although animal studies (Greiss, 1973) suggested a considerable reserve capacity of placental blood flow in a healthy fetus, an obstetric analgesic technique in clinical use should not reduce the intervillous blood flow (IBF).

Segmental extradural block using a small dose of bupivacaine (4 ml or 20 mg) during the first stage of labour increased the IBF slightly, but this was not statistically significant (Jouppila et al., 1978). However, knowledge of the effects on IBF of the clinically more popular lumbar extradural technique (8–10 ml of local anaesthetic) is lacking.

In current obstetric practice, bupivacaine and 2-chloroprocaine are the local analgesic drugs which offer safe and effective pain relief with virtually no neonatal side-effects (Finster and Pedersen, 1979). Joyce, Aquino and Kuchling (1976) demonstrated, in *in vitro* studies using gravid human uterine artery strips, that bupivacaine administered in clinical concentrations had a slight vasoconstrictive effect, whereas chloroprocaine produced vasodilatation. Fishburne, Hopkinson and Greiss (1977) showed in conscious pregnant sheep that bupivacaine infused i.a. decreased uterine blood flow (UBF) more than did 2-chloroprocaine. The decrease in UBF was a result of an increase in myometrial tone.

This study was performed to find out if the more extensive sympathetic block produced by the commonly used standard lumbar extradural technique changes IBF more than the low-dose segmental extradural analgesia, and if bupivacaine and 2-chloroprocaine differ in their effects on IBF when used for pain relief during the first stage of labour.

## PATIENTS AND METHODS

Twenty-six healthy patients were studied (table I); induction of labour between the 38th and 42nd weeks of pregnancy was planned and each had requested extradural analgesia. The indication for induction of labour was either a slightly post-term duration of the pregnancy or cervical maturation at term. Informed consent to the procedure was obtained from each patient and the study was approved by the Oulu University Ethics Committee. There were no signs of uteroplacental insufficiency. An anteriorly located placenta had been previously verified by an ultrasonic B-scan and its position marked on the abdominal skin with the mother lying in a 15° left lateral tilted position. All labours were induced by amniotomy or oxytocin infusion, or both. Each patient had been receiving oxytocin for at least 45 min before the first IBF measurement. At the time of commencement of extradural analgesia, the average cervical dilatation was 3.0 cm and the patients had regular painful contractions.

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TABLE I. *Details of patients studied. Group A=extradural bupivacaine; group B=extradural 2-chloroprocaine; group C=control.* *$P<0.05$

| Group | Age (yr) | Parity | Week of pregnancy | Birth weight | Apgar score 1 min | Apgar score 5 min |
|---|---|---|---|---|---|---|
| Group A ($n=10$) | | | | | | |
| Mean | 26.9* | 2.2 | 40.0 | 3797 | 8.4* | 9.2 |
| SD | ±2.8 | ±1.3 | ±1.2 | ±525 | ±0.9 | ±0.4 |
| Group B ($n=10$) | | | | | | |
| Mean | 21.3 | 1.4 | 40.7 | 3662 | 9.1 | 9.3 |
| SD | ±3.6 | ±0.5 | ±1.3 | ±676 | ±0.3 | ±0.5 |
| Group C ($n=6$) | | | | | | |
| Mean | 22.5 | 1.0 | 40.6 | 3495 | 8.8 | 9.3 |
| SD | ±2.4 | | ±0.5 | ±434 | ±0.4 | ±0.5 |

### *Analgesia*

Lumbar extradural analgesia was provided for pain relief immediately after the first IBF measurement. The first 10 mothers (group A) received 0.25% bupivacaine 10 ml (3 ml test dose and 7 ml after 5 min) through an extradural catheter inserted at the L2–3 interspace. Another 10 patients (group B) received 2% 2-chloroprocaine 10 ml (3 ml test dose). Six patients who received extradural analgesia after the second measurement of IBF were considered as a "non-extradural" control group (C). The mothers remained lying in a 15° left lateral position throughout the study period. They received Ringer lactate 500 ml within 30 min of the commencement of extradural analgesia (groups A and B). Group C patients received Ringer lactate 500 ml between the two IBF measurements (25 min). The effect of Ringer infusion on blood viscosity was measured in group C. Blood viscosity was determined from a 1.5-ml heparinized blood sample using a micro cone-plate viscometer LVT Well-Brookfield, Brookfield Engineering Laboratories Inc., Mass., U.S.A.) operating at 30 rev min$^{-1}$. The viscosity is expressed as cP (centipoise). Maternal arterial pressure was recorded with a standard sphygmomanometer at 5-min intervals for the first 30 min after the extradural injection. Fetal heart rate (by a scalp electrode) and uterine activity (by an intra-amniotic catheter) were monitored continuously on a cardiotocometer.

The analgesic effect of extradural block was good in all patients. The dermatome distribution of analgesia assessed immediately before the post-extradural IBF measurements ranged from T9 to L3.

### *Intervillous blood flow measurement*

The xenon-133 method used has been discussed in detail by Rekonen and others (1976). The control IBF ($IBF_1$) was measured immediately before the extradural injection (groups A and B). In group C, $IBF_1$ was measured immediately before starting Ringer lactate infusion. The second IBF measurement ($IBF_2$) was made 20–25 min after the commencement of the extradural block, when there was complete pain relief and skin analgesia to pinprick was as described above (group A and B). In group C, $IBF_2$ was measured 25 min after infusion of Ringer lactate was started and 500 ml had been infused. The scintillation detector was placed over and against the central part of the placenta (crystal-to-skin distance approx. 10 cm). Xenon-133 2 mCi in saline solution was rapidly injected to the antecubital vein through a two-way cannula and flushed immediately with saline 10 ml. To minimize the escape of xenon-133 bolus through the lungs, each patient exhaled and then held her breath for 15 s after the injection. Part of the bolus entered the systemic circulation and reached the placenta. The washout of the radio nuclide from the intervillous blood pool was monitored continuously for 10 min using a ratemeter and a recorder. The final flow-values were calculated by fitting the two-exponential function $c(t) = Ae^{-k_1t} + Be^{-k_2t}$ to the recorded curves and then $IBF = 100 \times k_1$ (ml min$^{-1}$ dl$^{-1}$). The results were analysed statistically using paired *t* test and Student's *t* test. $P < 0.05$ was considered significant.

## RESULTS

The data concerning the study population are shown in table I. The patients in group A were significantly older. The Apgar scores at 1 min were lower in group A than in groups B and C, but there was no neonatal depression in any group at any time (Apgar $> 7$ in all cases).

During 25 min Ringer lactate infusion blood viscosity decreased from 4.7 cP ± 0.6 to 4.4 cP ± 0.5 ($P < 0.01$). Uterine activity measured in Montevideo units (M.U.) decreased after the extradural block in both groups, from 152 ± 39 M.U. to 150 ± 29 M.U. in group A and from 156 ± 21 M.U. to 140 ± 20 M.U. in group B. Although the quantitative decrease in the uterine activity in both groups seems clinically unimportant, the percentage decrease in group B was statistically significant compared with the decrease in group A. If groups A and B are combined, there was a 9% decrease in uterine activity after the extradural block ($154 \pm 20$ M.U. to $145 \pm 16$ M.U.) but this was not statistically significant. In group C, uterine activity was $140 \pm 23$ M.U. immediately before IBF$_1$, and $135 \pm 23$ M.U. before IBF$_2$ (n.s.). There was no increase in uterine tone in any patient, nor was there maternal hypotension, defined as a systolic pressure less than 100 mm Hg or a 20% decrease in arterial pressure at any time.

The individual values of IBF$_1$, IBF$_2$ and the respective arterial pressures are shown in tables II, III and IV. Table V shows the mean values of IBF$_1$ and IBF$_2$ as well as the respective systolic arterial pressure values in groups A, B, A + B and C. There was no significant change in systolic arterial pressure in any group. Mean IBF decreased in the non-extradural group by 19% (n.s.); mean IBF increased by 37.5% in group A during extradural analgesia and by 35% in group B (fig. 1). The increase in IBF in groups A and B was, however, not statistically significant either within or between the two groups. However, when groups A and B were combined, the mean difference between IBF$_1$ and IBF$_2$ ($\Delta$ IBF) was $45 \pm 112$ ml min$^{-1}$ dl$^{-1}$. This increase in IBF after extradural analgesia was significant ($P < 0.05$). In control group C, five of six patients showed a decrease in IBF after Ringer infusion; a large increase of IBF was observed in the other patient in this group. Thus the comparison of the mean change in IBF between extradural and non-extradural groups ($A + B = 45 \pm 112$, $C = 31.5 \pm 121$ ml min$^{-1}$ dl$^{-1}$) showed no statistically significant difference ($P < 0.085$).

TABLE II. *Individual values of intervillous blood flow (IBF) (ml min$^{-1}$ dl$^{-1}$) and arterial pressure (mm Hg) in Group A before and during lumbar extradural analgesia*

| Patient No. | IBF$_1$ | IBF$_2$ | AP$_1$ | AP$_2$ |
|---|---|---|---|---|
| 1 | 241 | 326 | 135/80 | 110/70 |
| 2 | 76 | 184 | 140/80 | 130/80 |
| 3 | 327 | 355 | 110/80 | 110/70 |
| 4 | 164 | 145 | 130/80 | 140/80 |
| 5 | 161 | 483 | 120/80 | 115/75 |
| 6 | 164 | 283 | 130/90 | 120/80 |
| 7 | 353 | 323 | 130/90 | 130/90 |
| 8 | 261 | 254 | 120/80 | 120/80 |
| 9 | 211 | 122 | 130/80 | 130/70 |
| 10 | 346 | 398 | 100/70 | 110/70 |

TABLE III. *Individual values of intervillous blood flow (IBF) (ml min$^{-1}$ dl$^{-1}$) and arterial pressure (mm Hg) in group B before and during lumbar extradural analgesia. — = measurement failed*

| Patient No. | IBF$_1$ | IBF$_2$ | AP$_1$ | AP$_2$ |
|---|---|---|---|---|
| 1 | 131 | 169 | 130/80 | 120/80 |
| 2 | 293 | 245 | 140/80 | 140/80 |
| 3 | 316 | 173 | 130/70 | 120/70 |
| 4 | 103 | 356 | 130/80 | 130/80 |
| 5 | 180 | 187 | 135/100 | 140/100 |
| 6 | 78 | 60 | 120/50 | 120/70 |
| 7 | 218 | 286 | 100/60 | 110/60 |
| 8 | 145 | 291 | 120/75 | 120/70 |
| 9 | 278 | — | 110/60 | 100/60 |
| 10 | 172 | 154 | 120/80 | 120/60 |

TABLE IV. *Individual values of intervillous blood flow (IBF) (ml min$^{-1}$ dl$^{-1}$) and arterial pressure (mm Hg) in control group C before and immediately after pre-loading with Ringer lactate 500 ml (500 ml/25 min)*

| Patient No. | IBF$_1$ | IBF$_2$ | AP$_1$ | AP$_2$ |
|---|---|---|---|---|
| 1 | 263 | 96 | 120/80 | 110/80 |
| 2 | 75 | 267 | 120/75 | 135/80 |
| 3 | 141 | 93 | 140/85 | 140/85 |
| 4 | 152 | 113 | 130/80 | 140/80 |
| 5 | 218 | 114 | 120/70 | 110/60 |
| 6 | 107 | 84 | 115/65 | 100/70 |

TABLE V. *Mean (±SEM) values of IBF (ml min$^{-1}$ dl$^{-1}$) and systolic arterial pressure (mm Hg) in groups A, B and total study population (groups A + B) before and during extradural analgesia and in control group C*

| Group | IBF$_1$ | IBF$_2$ | AP$_1$ | AP$_2$ |
|---|---|---|---|---|
| A | $230 \pm 29$ | $287 \pm 61$ | $127 \pm 3.8$ | $125 \pm 3.8$ |
| B | $191 \pm 26$ | $213 \pm 29$ | $124 \pm 4.2$ | $123 \pm 4.4$ |
| A+B | $211 \pm 20$ | $252 \pm 25$ | $126 \pm 2.8$ | $124 \pm 2.8$ |
| C | $158 \pm 20$ | $128 \pm 20$ | $124 \pm 2.6$ | $123 \pm 5.1$ |

## DISCUSSION

In measuring the IBF, the diffusion of xenon-133 into the placenta tissue and the fetal circulation was not considered. However, diffusion from the intervillous blood pool is low and does not influence the results (Rekonen et al., 1976). After the i.v. injection of xenon-133, the bolus reaching the placenta is not an exact delta function, but has a right-skewed

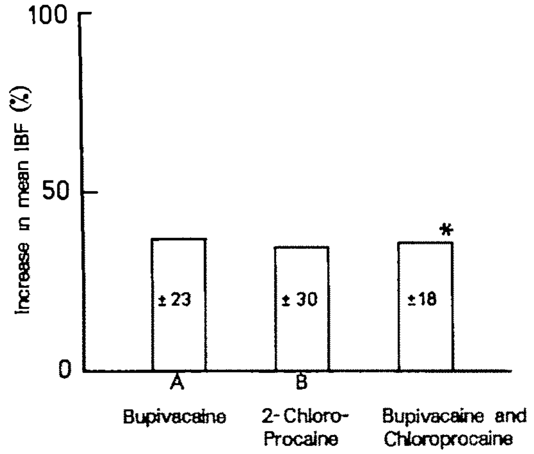

FIG. 1. Percent increase in mean IBF values (±SEM) after extradural analgesia. $*P<0.05$.

distribution with a half-life of 3–5 s. Recirculation of xenon-133 is minimal (A. Hollmén, 1979, personal communication). These factors have minimal effect on the clearance curve ($<10\%$). The reproducibility of the i.v. xenon-133 method has been good (Rekonen et al., 1976). In 24 paired measurements, the correlation between the first and second measurements was significant ($r=0.88$, $P<0.001$), and the mean of the differences was 6% with a standard deviation of 13%.

The advantages of the i.v. xenon-133 method include ease of performance and adequate reproducibility in consecutive measurements (Kuikka et al., 1978). The radiation dose to the fetus is negligible, being less than 1 mrad (Rekonen et al., 1976). The disadvantage is that blood flow is measured within a relatively small area of the placenta, expressed as flow per unit volume of placenta rather than total IBF. Even slight axial rotation of the uterus will alter the area of the placenta being measured. Since IBF is not uniform throughout the placenta (Kuikka et al., 1978), this will introduce errors between repeated measurements. To avoid any axial rotation of the uterus, the mother was maintained in exactly the same position between the two IBF measurements. We also marked the central part of the placenta and placed the scintillation detector carefully over that area, so that the measurement was made in the central part of the placenta which has a greater IBF, by an average of 55%, than the marginal parts (Kuikka et al., 1978).

The infusion of Ringer lactate 500 ml within 25 min between the measurements of $IBF_1$ and $IBF_2$ as in groups A and B could increase venous pressure, cardiac output and placental blood flow. A reduction in blood viscosity could also increase IBF. To ascertain the effect of a pre-load as used in groups A and B, we measured blood viscosity and IBF immediately before pre-load and after the infusion of Ringer lactate 500 ml (group C). There was a slight but statistically significant decrease in blood viscosity. However, the IBF showed a slightly decreasing trend in five of six patients, although this was not statistically significant.

Extradural analgesia with either chloroprocaine or bupivacaine slightly increased the IBF. There was no significant difference in the effects on intervillous blood flow between these drugs. When the two groups were combined, a statistically significant improvement of IBF during extradural anagelsia was observed. A comparison of these IBF data with our earlier study (Jouppila et al., 1978), in which we used exactly the same technique in a comparable group of patients, shows that an increase of the volume of the local anaesthetic (bupivacaine) from 4 ml to 10 ml nearly doubled the mean percentage increase of IBF (18 ± 28 and 36.4 ± 18 respectively). It is interesting that we were able to demonstrate the same trend in toxaemic patients, in whom bupivacaine 4 ml improved IBF slightly (30% ± 54), whereas a 10-ml dose led to an increase of 80% (± 82) (Jouppila et al., 1979). Thus it seems that a more extensive sympathetic block produces a greater improvement in IBF. Janisch and others (1978), using an i.v. bolus radioisotope technique, also noted an improvement of IBF during extradural analgesia in five toxaemic patients, although their patients were not in labour. They suggested that the improvement in IBF was produced by a reduction in arterial spasm and myometrial relaxation. In the present study, however, we observed no change in the uterine tone. Husemeyer and Crawley (1979) were unable to establish statistically significant changes in IBF during lumbar extradural analgesia. They measured the IBF by the xenon-133 inhalation method. The patient took three slow breaths (30 s) from a reservoir bag which contained xenon-133 2 mCi in oxygen 2 litre. The slow inhalation involved with this technique means that the isotope reaches the uterus over a prolonged period, which makes the technique more sensitive to the effects of recirculation than the rapid i.v. bolus injection used in our study. The lower IBF control values in Husemeyer and Crawley's series could be explained partially by the differences in patients (healthy in our series, but high-risk in theirs) and the fact that the absence of preloading led to a significant decrease in mean arterial pressure in their study. A principal difference between the studies is that we performed the measurements during active labour, whereas Husemeyer and Crawley measured the effects of extradural analgesia on IBF before the induction of labour. The studies made before and during active labour indicate that measurements performed between successive uterine contractions generally give greater values for IBF than measurements made before active labour (Jouppila et al., 1978; Käär et al., 1978). Therefore it is questionable to compare IBF values obtained before and during active labour.

In our study, maternal arterial pressure (uterine perfusion pressure) remained stable, and neither the uterine activity nor the uterine tone (extrinsic myometrial tone) changed significantly during the time taken to perform the two IBF measurements. The improvement in IBF during extradural analgesia is therefore presumably caused by decreased intrinsic vasomotor tone of uteroplacental vessels. The finding that not only pain relief, but a more extensive extradural block is needed for a significant improvement in IBF, suggests that pain relief in itself and its possible inhibitory effects on the release of humoral vasoconstrictive substances (catecholamines) cannot alone explain the increase in IBF. Another factor decreasing the uteroplacental vascular resistance seems to be the sympathetic block caused by extradural analgesia.

2-Chloroprocaine and bupivacaine do not differ in their effects on the IBF. When a 10-ml dose of either drug was used during lumbar extradural analgesia, there was a significant improvement in IBF in healthy parturients. This improvement could be of importance in obstetric high-risk patients, for example toxaemic parturients, in whom IBF is primarily reduced and the oxygen delivery to the fetus compromised.

## REFERENCES

Finster, M., and Pedersen, H. (1979). Placental transfer and fetal uptake of drugs. *Br. J. Anaesth.*, 51, 255.

Fishburne, J. I. jr, Hopkinson, R. B., and Greiss, F. C. jr (1977). Responses of the gravid uterine vasculature to arterial levels of local anesthetic agents. Abstr. Annual Society of Obstetrical Anesthesia and Perinatology Meeting, p. 37.

Greiss, F. C. jr (1973). Concepts of uterine blood flow; in *Obstetrics and Gynecology Annual*, Vol. 2, p. 53. New York: Appleton–Century–Crofts.

Husemeyer, R. P., and Crawley, J. C. W. (1979). Placental intervillous blood flow measured by inhaled $^{133}$Xe clearance in relation to induction of epidural analgesia. *Br. J. Obstet. Gynaecol.*, 86, 426.

Janisch, H., Leodolter, S., Neumark, J., and Philipp, K. (1978). Der Einfluss der kontinuerlichen Epiduralanästhesie auf die utero-placentare Durchblutung. *Z. Geburtsh. u. Perinat.*, 182, 346.

Jouppila, R., Jouppila, P., Hollmén, A., and Kuikka, J. (1978). Effect of segmental extradural analgesia on placental blood flow during normal labour. *Br. J. Anaesth.*, 50, 563.

——— ——— ——— Vierola, H., and Koivula, A. (1979). Effect of epidural analgesia on placental blood flow in hypertensive pregnancies. Abstr. 15th Congress of The Scandinavian Society of Anaesthesiologists, Odense, Denmark.

Joyce, T. H., Aquino, N., and Kuchling, A. (1976). The effect of local anesthetics on gravid human uterine artery strips *in vitro*. Abst. Sci. Papers, p. 359. American Society of Anesthesiologists.

Käär, K., Jouppila, P., Kuikka, J., Luotola, H., Toivanen, J., and Rekonen, A. (1978). Intervillous blood flow in normal and complicated late pregnancy measured with an intravenous $^{133}$Xe method. *Acta Obstet Gynaecol. Scand.*, (in press).

Kuikka, J., Käär, K., Jouppila, P., Pyörälä, T., and Rekonen, A. (1978). An intravenous $^{133}$Xe method for measuring vaginal distribution of placental blood flow. *Acta Obstet. Gynaecol. Scand.*, 57, 249.

Rekonen, A., Luotola, H., Pitkänen, M., Kuikka, J., and Pyörälä, T. (1976). Measurement of intervillous and myometrial blood flow by an intravenous $^{133}$Xe method. *Br. J. Obstet. Gynaecol.*, 83, 723.

## EFFET D'UNE ANESTHESIE PERIDURALE A LA BUPIVACAINE ET A LA 2-CHLOROPROCAINE SUR LE DEBIT SANGUIN INTERVILLEUX AU COURS DE TRAVAIL NORMAL

### RESUME

Les effets d'une analgésie péridurale lombaire sur le débit sanguin intervilleux (DSI), au cours du travail, ont été étudiés chez 26 parturientes en bonne santé grâce à une injection i.v. rapide de xenon-133. Il y eut une diminution de 19% du DSI moyen chez six parturientes (du groupe témoin, sans péridurale). Le DSI moyen augmentait de 37,5% avec 10 ml de bupivacaïne 0,25% et de 35,2% avec 10 ml de 2-chloroprocaïne à 2%. Si l'on regroupe les deux séries de péridurales, la différence moyenne $DSI_1$ et $DSI_2$ était de $45 \pm 112$ ml min$^{-1}$ dl$^{-1}$. Cette augmentation est statistiquement significative ($P < 0,05$). L'amélioration du DSI, après un bloc péridural, a été considérée comme le résultat d'une diminution des résistances vasculaires utérines, dans la mesure où aucune modification significative de pression artérielle, d'activité uterine ou de tonus utérin n'a eté observee.

## AUSWIRKUNG DER PERIDURALANÄSTHESIE MIT BUPIVACAIN UND 2-CHLOROPROCAIN AUF DIE INTRAVILLÖSE DURCHBLUTUNG WÄHREND DER NORMALEN GEBURT

### ZUSAMMENFASSUNG

Die Auswirkung der lumbalen Periduralanästhesie auf die intravillöse Durchblutung (IBF) wurde ab 26 gesunden Gebärenden mittels eines i.v. Bolus von Xenon-133 untersucht. Die mittlere IBF nahm bei 6 Gebärenden um 19% ab (nicht-peridurale Kontrollgruppe). Die mittlere IBF nahm um 37,5% zu, wenn 0,25% Bupivacain 10 ml und um 35,2%, wenn 2% 2-chloroprocain 10 ml benutzt wurden. Beim Zusammenlegen der zwei periduralen Gruppen war die mittlere Differenz zwischen $IBF_1$ und $IBF_2$ 45 ± 112. Diese Zunahme ist statistisch signifikant ($P < 0,05$). Die Verbesserung der IBF nach dem Periduralblock wird als Folge des herabgesetzten Gefäßwiderstandes angesehen, da keine signifikanten Veränderungen des arteriellen Druckes und der Aktivität oder des Tonus des Uterus zu messen war.

## EFECTO DE LA ANALGESIA EXTRADURAL EN BASE A BUPIVACAINA Y 2-CLOROPROCAINA SOBRE LA CORRIENTE SANGUINEA INTERVELLOSA DURANTE EL PARTO NORMAL

### SUMARIO

Se estudió el efecto de la analgesia extradural lumbar sobre la corriente sanguínea intervellosa (IBF) durante el parto de 26 parturientas sanas con las cuales se usó una inyección de tazón i.v. de Xenón-133. Hubo una disminución del 19% (n.s.) del IBF promedio en seis parturientas (grupo de control no-extradural). El IBF promedio aumentó en un 37,5% cuando se usó 10 ml de bupivacaina al 0,25% y en un 35,2% cuando se empleó 10 ml de 2-cloroprocaina al 2% (n.s.). Cuando se combinó a los dos grupos extradurales, la diferencia promedia entre $IBF_1$ y $IBF_2$ era de 45 ± 112. Este aumento es significante desde el punto de vista estadístico ($P < 0,05$). El mejoramiento del IBF después del bloqueo extradural se consideró como siendo el resultado de una resistencia vascular uterina reducida, puesto que no se observó ningún cambio significante en la presión arterial, ni tampoco en la actividad uterina o en el tono uterino.

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# PLASMA PHARMACOKINETICS OF MORPHINE AFTER I.M., EXTRADURAL AND INTRATHECAL ADMINISTRATION

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## SUMMARY

Eighteen patients received morphine 0.2 mg kg$^{-1}$ in 0.9% saline i.m. ($n = 6$), extradurally ($n = 6$), or in a 10% dextrose solution intrathecally ($n = 6$) for pain relief after operation. Plasma unmetabolized morphine was isolated by extraction using liquid–solid chromatography and measured by radioimmunoassay. Conjugated morphine was calculated from the difference between total immunoreactive morphine and unmetabolized morphine. Initial vascular absorption was significantly less in the intrathecal group than in the i.m. and extradural groups. This accounts for persistence of plasma unmetabolized morphine at 24 h and for more prolonged analgesia in the intrathecal group. Prolonged analgesia observed following extradural and intrathecal administration was caused by a small quantity of unmetabolized morphine. Extradural and i.m. groups showed the same pharmacokinetic patterns although extradural analgesia is much more prolonged. Morphine glucuronide appeared later in blood in the intrathecal group than in the two other groups.

The initial rate of vascular absorption of morphine following intrathecal administration is slower than after i.m. or extradural injections which have a similar rate (Chauvin et al., 1981). However, a non-specific radioimmunoassay was used in that study which measured both unmetabolized and conjugated morphine and which made it impossible to interpret the increased plasma morphine concentrations observed several hours after morphine administration. Serum concentrations of unconjugated morphine base have been determined previously after extradural administration (Weddel and Ritter, 1981), but the authors did not compare this technique with i.m. and intrathecal morphine. We have determined serum concentrations of unconjugated morphine base after i.m., extradural and intrathecal administration of the same doses of morphine.

## METHODS

Eighteen patients with severe pain following surgery were studied. All gave informed consent. The patients were allocated to three groups and received 0.2 mg kg$^{-1}$ morphine hydrochloride in 0.9% saline i.m. ($n = 6$), extradurally ($n = 6$), or in 10% dextrose solution intrathecally ($n = 6$). The volume of the solution injected was always 2 ml.

Plasma unmetabolized morphine was isolated by extraction using liquid–solid chromatography and measured by radioimmunoassay. The experimental procedure consists of isolation of morphine from its main metabolites (glucuroconjugates). A 0.5-ml plasma aliquot was diluted with 1.5 ml of buffer (disodium tetraborate 0.01 mol litre$^{-1}$, pH 9.0), added to an extraction column filled by a Kieselgur (Extrelut, Merck), and chromatographed for 30 min. Ten millilitre of ethyl acetate was used to elute the unmetabolized morphine fraction. The eluate was then dried at 50°C under nitrogen. The residue was dissolved in 0.5 ml of buffer (sodium phosphate 0.01 mol litre$^{-1}$, pH 7.0) and thoroughly mixed by vortexing (yield between 81% and 88%).

Morphine was measured by radioimmunoassay using $^{125}$I-labelled morphine (Kit Abuscreen, Roche Diagnostics, Hoffman-La-Roche, Inc., Nutley, N. J.). The procedure was performed according to the manufacturer's instructions for the quantitative determination of morphine in plasma. Conjugated morphine was calculated from the difference between total immunoreactive morphine and unmetabolized morphine. Measurements were performed before and 2, 10, 15 and 30 min, 1, 2, 3, 4, 5, 6, 9, 12 (i.m. group) 18 and 24 h (extradural and intrathecal groups) following morphine injections. Pharmacokinetic data were calculated: maximum concentration ($C_{P\,max}$), time to $C_{P\,max}$ ($t_{max}$) and the

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area under the curve (AUC) at 12 h measured by planimetry.

Data were expressed as mean ± SEM and statistical analyses performed using the non-parametric Fisher test.

## RESULTS

All patients had undetectable serum concentrations immediately before morphine administration. Figure 1 shows that plasma concentrations of unmetabolized morphine following intrathecal administration were significantly less than after i.m. ($P < 0.01$) at 2 (2 ± 1, 26 ± 6 ng ml$^{-1}$ respectively), 10 (18 ± 7, 52 ± 6 ng ml$^{-1}$), 15 (24 ± 7, 51 ± 6 ng ml$^{-1}$), 30 (27 ± 5, 51 ± 5 ng ml$^{-1}$) and 60 min (25 ± 3, 44 ± 6 ng ml$^{-1}$) or extradural administration ($P < 0.05$) at 2 (36 ± 12 ng ml$^{-1}$), 10 (48 ± 12 ng ml$^{-1}$), 15 min (46 ± 5 ng ml$^{-1}$) and 30 min (39 ± 15.3 ng ml$^{-1}$). One hour after administration, plasma concentrations of unmetabolized morphine were still less in the intrathecal group than in the extradural group (26 ± 6, 32 ± 4 ng ml$^{-1}$). However, this difference was not statistically significant. From the 3rd hour, the plasma concentration of unmetabolized morphine was greater in the intrathecal group and these differences were statistically significant compared with the i.m. group ($P < 0.01$) at 9 and 12 h and with the extradural group ($P < 0.05$) at 12, 18 and 24 h.

Table I shows the pharmacokinetic data. I.m. and extradural groups had similar $C_{P\,max}$, $t_{max}$ and AUC. The intrathecal group had smaller $t_{max}$ and $C_{P\,max}$ than i.m. group ($P < 0.03$). In the extradural group, only $t_{max}$ was significantly greater than in the intrathecal group ($P < 0.03$). Conjugated morphine concentration increased progressively during the 1st hour and was similar to unmetabolized morphine concentration at 1–2 h in all patients (fig. 2). Morphine glucuronide appeared at 10 min in the extradural and i.m. groups and at 30 min in the intrathecal group. At 24 h, the plasma concentrations of morphine glucuronide were increased in all groups.

TABLE I. *Plasma pharmacokinetic parameters after i.m., intrathecal and extradural adminstration of morphine hydrochloride 0.2 mg kg$^{-1}$ (mean ± SD).* † $P < 0.03$ *i.m.* v. *intrathecal groups;* ‡ $P < 0.03$ *extradural* v. *intrathecal groups*

| Route of administration | *n* | $C_P$ max (ng ml$^{-1}$) | *t* max (h) | AUC at 12 h (ng ml$^{-1}$ h$^{-1}$) |
|---|---|---|---|---|
| I. m. | 6 | 60.0 ± 6.2† | 0.43 ± 0.31† | 165.2 ± 74.8 |
| Intrathecal | 6 | 35.2 ± 10.2 | 1.65 ± 1.18 | 282.3 ± 269 |
| Extradural | 6 | 50.3 ± 20.5 | 0.23 ± 0.15‡ | 177.9 ± 39.9 |

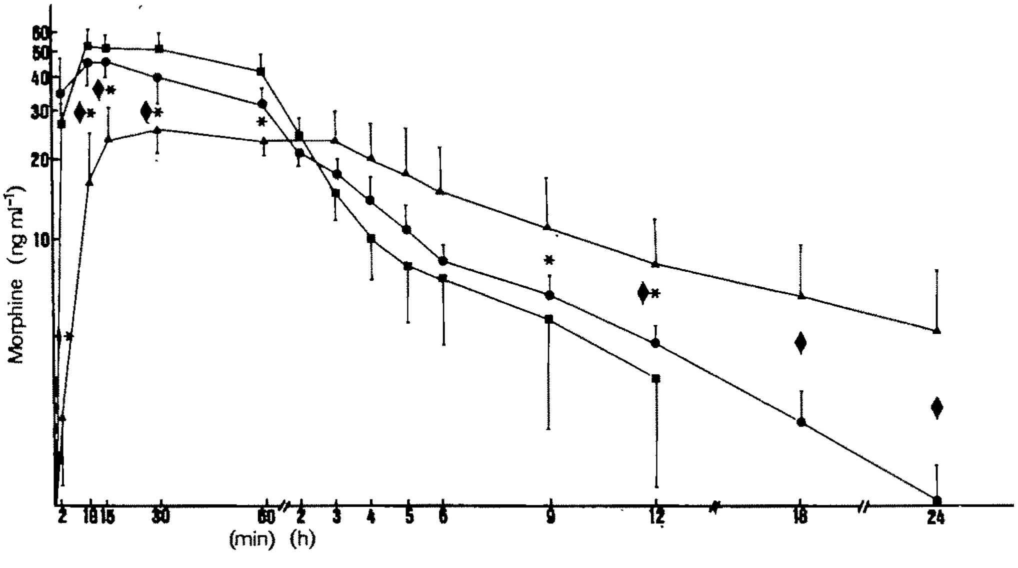

FIG. 1. Plasma concentration of unmetabolized morphine after i.m. (■), extradural (●) and intrathecal (▲) injection of morphine 0.2 mg kg$^{-1}$ (mean ± SEM). *$P < 0.02$, i.m. *v.* intrathecal groups; (◆) $P < 0.05$, extradural *v.* intrathecal groups.

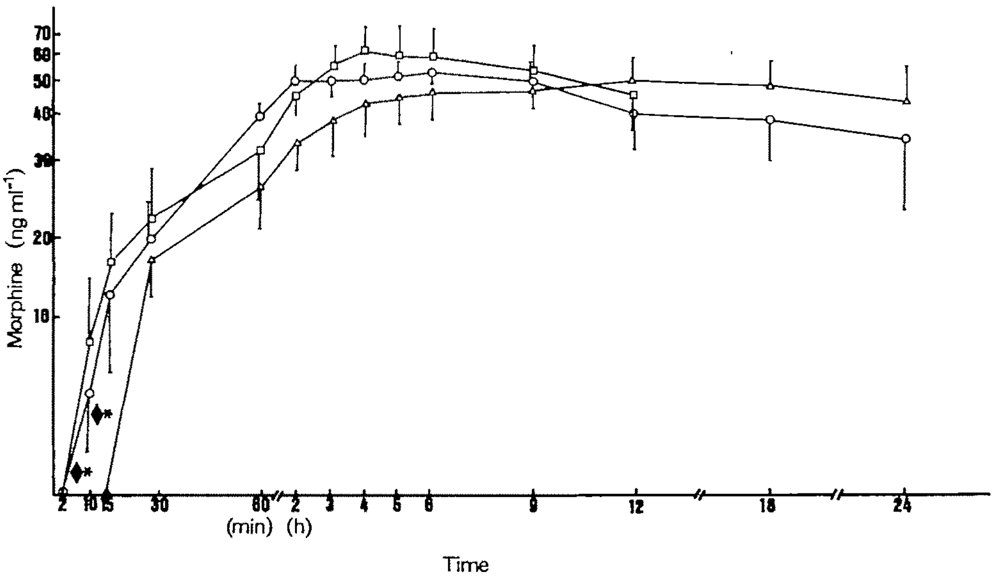

FIG. 2. Plasma concentration of conjugated morphine after i.m. (□), extradural (○) and intrathecal (△) injection of morphine 0.2 mg kg$^{-1}$ (mean ± SEM). *$P < 0.01$ i.m. $v$. intrathecal groups; (♦) $P < 0.01$ extradural $v$. intrathecal groups.

## DISCUSSION

During the first 30 min, plasma concentrations in the three groups are largely composed of unmetabolized morphine, which confirms that non-specific radioimmunoassay is adequate to estimate the speed of initial vascular absorption of morphine (Chauvin et al., 1981). Afterwards, morphine glucuronide concentrations increase rapidly. Berkowitz (1976) had already observed the same relationship between serum morphine and morphine glucuronide following i.m. administration. Thus, it is necessary to measure unconjugated morphine to interpret the high plasma concentrations of immunoreactive morphine observed after 1–2 h.

Our data show that morphine given i.m. and extradurally has a similar rate of vascular absorption and that plasma pharmacokinetics are the same. This similarity of distribution of morphine administered by these routes produces a similar metabolism of morphine which is confirmed by the similar morphine glucuronide concentration–time profiles. Such similarity contrasts with the prolonged analgesia which has been reported following extradural morphine (Behar et al.,1979; Magora et al., 1980). Indeed, extradural analgesia is probably caused by the diffusion of a small quantity of morphine across the dura into cerebrospinal fluid (c.s.f.) and therefore, is not detectable in the plasma pharmacokinetics. However, this small quantity of morphine is still larger than the fraction able to penetrate within the central nervous system following i.m. administration (Kufferberg and Way, 1963) and is slowly resorbed from c.s.f. because of its low lipid solubility (Kaufman, Semo and Koski, 1975) and thus is able to produce prolonged analgesia.

However, there are differences between the intrathecal and the other two methods of administration on distribution of morphine. The initial rate of vascular absorption of morphine is much slower following intrathecal administration than after i.m. or extradural injection. $t_{\max}$ values confirm these data and the appearance of morphine glucuronide in blood is delayed following intrathecal administration. Later, the rate of vascular absorption of morphine becomes greater in the intrathecal group than in the other two groups. This persistence of unconjugated morphine in plasma at 24 h is consistent with the presence of a small quantity of morphine in the subarachnoid space. This is enough to account for more prolonged analgesia. With extradural administration, there is no unconjugated morphine left in plasma at 24 h, which is consistent with the absence of morphine in the subarachnoid space and loss of analgesia. Analgesia always lasted less than 6 h after i.m. administration and more than 12 h after extradural and intrathecal administration

(Samii, Chauvin and Viars, 1981). However, AUC 12 h after morphine administered i.m. was not superior to that of morphine administered extradurally and intrathecally. This confirms that the prolonged analgesia observed following extradural and intrathecal administration is caused by a small quantity of unconjugated morphine which is undetectable on classical plasma pharmacokinetic measurements such as AUC. Indeed, it has been demonstrated that a smaller dose of morphine given intrathecally (Wang, Nauss and Thomas, 1979) is sufficient to produce potent analgesia. Therefore we used larger doses to compare a similar dose of morphine (0.2 mg $kg^{-1}$) in the three groups of patients. Such large doses of intrathecal morphine are not necessary and may induce respiratory depression (Samii, Chauvin and Viars, 1981).

In conclusion, morphine has a slower rate of vascular absorption following intrathecal administration than after i.m. or extradural administration. This confirms results of a previous study using radioimmunoreactive morphine. Morphine given by i.m. and extradural routes has similar plasma concentrations, but analgesia is more prolonged following the latter route. Plasma morphine concentrations are small at 24 h after intrathecal administration although analgesia persists. Thus, only a small fraction of extradurally and intrathecally administered morphine is left on spinal opiate receptors to achieve prolonged analgesia.

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## REFERENCES

Behar, M., Olshwang, D., Magora, F., and Davidson, J. J. (1979). Epidural morphine in treatment of pain. *Lancet*, 1, 527.

Berkowitz, B. A. (1979). The relationship of pharmacokinetics to pharmacological activity: morphine, methadone and naloxone. *Clin. Pharmacokin.*, 1, 219.

Chauvin, M., Samii, K., Schermann, J. M., Sandouk, P., Bourdon, R., and Viars, P. (1981). Plasma concentration of morphine after i.m. extradural and intrathecal administration. *Br. J. Anaesth.*, 53, 911.

Kaufman, J. J., Semo, N. M., and Koski, W. S. (1975). Microeletrometric titration measurement of the pKa's and partition and drug distribution coefficients of narcotics and narcotic antagonists and their pH and temperature dependance. *J. Med. Chem.*, 18, 647.

Kufferberg, R., and Way, L. (1963). Pharmacologic basis for the increased sensitivity of the new-born rat to morphine. *J. Pharmacol. Exp. Ther.*, 141, 106.

Magora, F., Olshwang, D., Eimerl, D., Shorr, J., Katzenelson, R., Cotev, S., and Davidson, J. J. (1980). Observations on extradural morphine analgesia in various pain conditions. *Br. J. Anaesth.*, 52, 247.

Samii, K., Chauvin, M., and Viars, P. (1981). Postoperative spinal analgesia with morphine. *Br. J. Anaesth.*, 53, 817.

Wang, J. K., Nauss, L. A., and Thomas, J. E. (1979). Pain relief by intrathecally applied morphine in man. *Anesthesiology*, 50, 149.

Weddel, S. J., and Ritter, R. R. (1981). Serum levels following epidural administration of morphine and correlation with relief of postsurgical pain. *Anesthesiology*, 54, 210.

## PHARMACOCINETIQUE PLASMATIQUE DE LA MORPHINE APRÈS ADMINISTRATION PAR VOIES INTRAMUSCULAIRE, PERIDURALE ET INTRATHECALE

### RESUME

On a administré à 18 patients 0,2 mg $kg^{-1}$ de morphine dans une solution salée à 0,9% par voie intramusculaire ($n = 6$), par voie péridurale ($n = 6$) et dans une solution de dextrose à 10% par voie intrathécale ($n = 6$) pour soulager les douleurs post-opératoires. La morphine non-métabolisée a été isolée du plasma par une méthode d'extraction utilisant la chromatographie liquide–solide, puis mesurée par radio-immunologie. La morphine glycuroconjuguée a été calculée par différence entre la morphine totale immunoréactive et la morphine non-métabolisée. La résorption sanguine initiale de la morphine est significativement plus basse pour la voie intrathécale que pour les deux autres voies. Ceci explique que la voie intrathécale présente les taux sanguins tardifs les plus élevés et une analgésie plus prolongée. Pour les deux voies d'administration médullaires, la quantité de morphine susceptible d'induire une analgésie de longue durée doit être faible. Les voies péridurale et intramusculaire présentent une pharmacocinétique plasmatique identique bien que l'analgésie par voie péridurale soit nettement plus prolongée. Le dérivé glycuroconjugué apparait plus vite dans le sang, pour les voies péridurale et intramusculaire que pour la voie intrathécale.

## DIE PHARMAKOKINETIK DES MORPHIUMS IM PLASMA NACH I.M., EXTRADURALER UND INTRATHEKALER ANWENDUNG

### ZUSAMMENFASSUNG

Achtzehn Patienten erhielten Morphium 0,2 mg $kg^{-1}$ in 0,9% Kochsalz i.m. ($n = 6$), extradural ($n = 6$) oder in 10%iger Dextroselösung intrathekal zur postoperativen Schmerzbekämpfung. Das nicht metabolisierte Morphium im Plasma wurde durch Extraktion in Flüssigkeits-Chromatographie isoliert und mittels Radioimmunoassay gemessen. Das konjugierte Morphium wurde berechnet aus der Differenz zwischen totalem immunoreaktiven Morphium und nicht metabolisiertem Morphium. Die anfängliche vaskuläre Absorption war bei der intrathekalen Gruppe signifikant geringer als in der i.m. und extraduralen Gruppe. Dies ist der Grund für das Verbleiben von nicht metabolisiertem Morphin im Plasma über 24 Stunden und für die verlängerte Analgesie in der intrathekalen Gruppe. Die nach extraduraler und intrathekaler Anwendung beobachtete verlängerte Analgesie war durch eine kleine Menge von nicht metabolisiertem Morphium hervorgerufen. Die extradurale und

die i.m. Gruppe zeigten dieselben pharmakokinetischen Muster, obwohl die extradurale Analgesie viel länger dauert. Morphiumglucuronid erschien später im Blut in der intrathekalen Gruppe als in den zwei anderen Gruppen.

## FARMACOCINATICAS DEL PLASMA DESPUES DE LA ADMINISTRACION INTRAMUSCULAR, EXTRADURAL E INTRATECAL DE MORFINA

### SUMARIO

Se administraron 0,2 mg $kg^{-1}$ de morfina en una solución salina intramuscular al 0,9% (n = 6), extraduralmente (n = 6) en una solución dextrosa al 10%, así como intratecalmente (n = 6), a 18 pacientes después de someterlos a intervención quirúrjica y para fines de alivio del dolor. Se aisló del plasma la morfina no metabolizada, mediante extracción, haciendo uso de cristalografía líquido-solida y efectuando las medidas por medio de radioinmunoensayos. La morfina conjugada se calculó mediante la diferencia entre la morfina inmunoreactiva total y la que no fue metabolizada. La absorción vascular inical fue significativamwente inferior en el grupo intratecal que en los grupos de administración intramuscular y extradural. Esto justifica el que siguiera habiendo plasma sin metabolizar al cabo de las 24 horas y la analgesia más prolongada en el grupo intratecal. La analgesia prolongada que se observó a raiz de la administración extradural e intratecal fue ocasionada por una pequeña cantidad de morfina sin metabolizar. Los grupos extradural e intramuscular mostraron los mismos modelos farmacocinéticos, aunque la analgesia extradural es mucho más prolongada. Glucorodina de morfina apareció posteriormente en la sangre del grupos intratecal en mayor cantidad que en los otros dos grupos.

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# KINETICS OF HIGH-DOSE I.V. DIAZEPAM

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## SUMMARY

The pharmacokinetics of high-dose i.v. diazepam were studied in two patients in an intensive care unit. The first patient received up to 240 mg of diazepam daily for 21 days while the second received 60 mg daily for 30 days. Plasma concentrations of diazepam and its major metabolite, desmethyldiazepam, were very large but, despite severe underlying disease and simultaneous administration of several other drugs, the half-lives of diazepam and desmethyldiazepam washout were consistent with those found in healthy persons. Washout half-lives in the first patient were, if anything, shorter than expected, possibly caused by simultaneous administration of phenobarbitone. Thus the kinetics of diazepam are apparently not altered by administration of large doses.

The kinetics of i.v. diazepam have been studied following single therapeutic doses in humans (Klotz et al., 1975; Mandelli, Tognoni, and Garattini, 1978; Greenblatt et al., 1980; Ochs et al., 1981a). However, very large doses of diazepam may be administered i.v. to patients for sedation in the intensive care unit (ICU). Little information is available on plasma diazepam concentrations or diazepam disposition in these circumstances. The report and study of diazepam kinetics and clinical effects during and after administration of very large doses i.v. to patients in an ICU.

## CASE REPORTS

### *Patient 1*

A 54-yr-old man was admitted to the intensive care unit with severe tetanus. Because of uncontrollable muscle spasticity and agitation pancuronium was given to allow tracheal intubation and assisted ventilation. During the first 21 days the patient received numerous drugs including fentanyl, biperiden (an anticholinergic agent), droperidol, promethazine, chlorpromazine, pethidine and a mixture of ergot alkaloids. The patient also received multiple i.v bolus doses of diazepam ranging from 60 to 240 mg per day (fig. 1). The doses were reduced and discontinued by day 21. In an attempt to enhance the elimination of diazepam and its metabolite by enzyme induction, phenobarbitone (up to 240 mg per day) was administered from day 14 to day 21.

Multiple venous blood samples were drawn from an indwelling central venous cannula during and after the period of diazepam administration.

### *Patient 2*

A 43-yr-old man with chest trauma, and renal insufficiency which required haemodialysis, was admitted to the intensive care unit. To produce sedation for assisted ventilation, the patient received 60 mg daily of i.v. diazepam in multiple bolus doses for a period of 30 days. Additional drugs administered included dobutamine, cimetidine, gentamicin and opiate analgesics. Multiple venous blood samples were drawn from a central venous cannula over the 12 days after diazepam discontinuation.

Concentrations of diazepam and its major metabolite, desmethyldiazepam, were determined in all samples by electron-capture gas–liquid chromatography (Greenblatt, 1978; Greenblatt, Ochs and Lloyd, 1980). The apparent half-life for disappearance of diazepam and desmethyldiazepam after termination of dosage was determined by linear regression analysis.

## RESULTS

### *Patient 1*

Concentrations of diazepam and its major metabolite, desmethyldiazepam, were very large, consistent with the large daily doses (fig. 1.). Steady-state plasma concentrations ranged from

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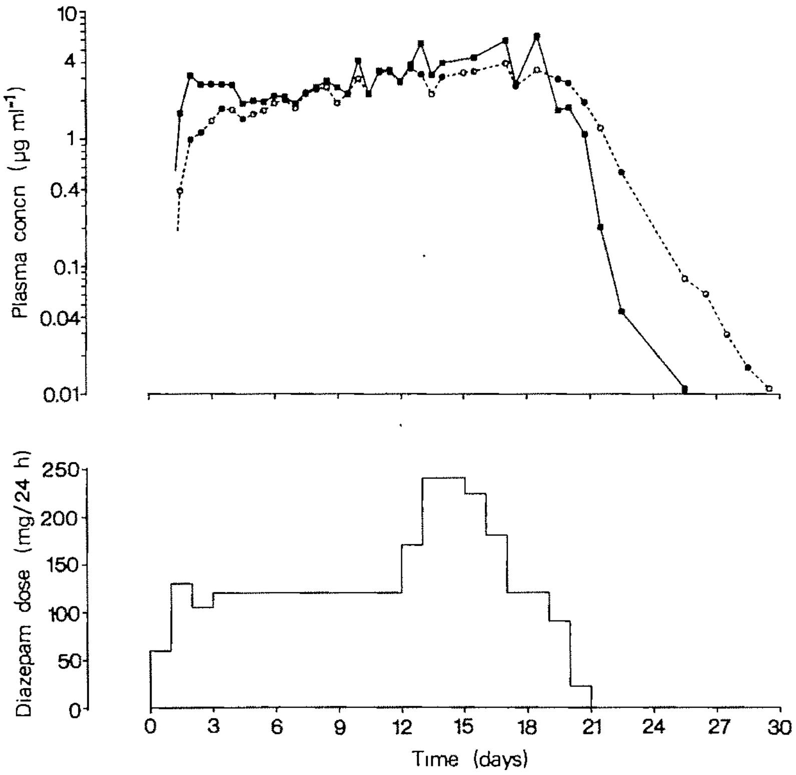

FIG. 1. Plasma concentrations of diazepam (■——■, $T_{\frac{1}{2}}$= 17 h) and desmethyldiazepam (O---O, $T_{\frac{1}{2}}$ = 28 h), and daily dose of diazepam, in the first patient. Post-dose washout half-lives were determined by least-squares regression analysis ($r^2$ = 0.98 and 0.99 for diazepam and desmethyldiazepam, respectively).

1000 to more than 5000 ng ml$^{-1}$, and increased approximately in proportion to the daily dose. After termination of diazepam therapy, the apparent half-life of diazepam "washout" was 17 h and that of desmethyldiazepam was 28 h.

Central nervous system (c.n.s.) depression persisted after diazepam therapy was stopped and spontaneous ventilation did not resume until 7 days after diazepam was discontinued. Similarly, the patient did not become fully oriented until 7–10 days after diazepam had been stopped. He was discharged from the hospital 20 days after discontinuation of diazepam (after 40 days of hospital treatment).

### *Patient 2*

Large concentrations of diazepam (400–800 ng ml$^{-1}$) and of desmethyldiazepam (1000–5000 ng ml$^{-1}$) were achieved after administration of diazepam (fig. 2). After discontinuing diazepam treatment, the apparent half-life of diazepam washout was 43 h and that of desmethyldiazepam 78 h.

## DISCUSSION

Large doses of i.v. diazepam were required to produce satisfactory sedation in these severely ill, agitated patients. Daily doses of up to 10 times the usual range for anxiolytic or muscle relaxant therapy were administered. Steady-state plasma concentrations were correspondingly large compared with those measured during prolonged therapy with usual doses (Greenblatt et al., 1981). However, large concentrations were necessary to produce adequate sedation in these severely agitated patients (Dasta et al., 1981). There was no evidence that these doses and plasma concentrations of diazepam and its major metabolite were associated with any untoward cardiovascular depression.

In the first patient, phenobarbitone was administered simultaneously in an attempt to enhance

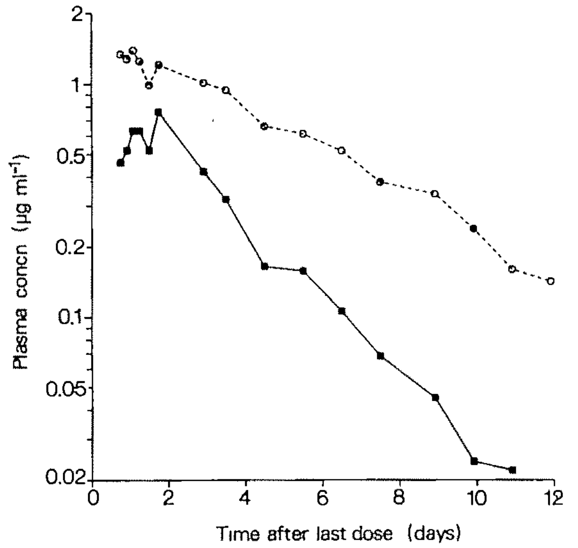

FIG. 2. Plasma concentrations of diazepam (■——■, $T_{\frac{1}{2}} = 43$ h) and desmethyldiazepam (○- - -○, $T_{\frac{1}{2}} = 78$ h) after termination of diazepam dosage in the second patient. Values of washout half-life were determined by least-squares regression analysis ($r^2 = 0.88$ and 0.99 for diazepam and desmethyldiazepam, respectively).

diazepam elimination and thereby reduce the likelihood of prolonged c.n.s. depression previously reported following long-term high-dose diazepam therapy of tetanus (Kendall and Clarke, 1972; Odusote, George and Femi-Pearse, 1976). Half-lives of diazepam and desmethyldiazepam washout after termination of administration were 17 and 28 h, respectively. The usual range of diazepam elimination half-life in otherwise healthy young males is 20–70 h, with a prolongation of half-life observed with increasing age (Klotz et al., 1975; Greenblatt et al., 1980; Ochs et al., 1981a). For desmethyldiazepam, the usual range is 40–140 h, again with a prolongation observed in the elderly (Allen et al., 1980; Shader et al., 1981). Thus, washout of the two drugs in this patient was in fact more rapid than that generally observed in single-dose pharmacokinetic studies, suggesting that elimination was enhanced by the enzyme-inducing effects of phenobarbitone (Ohnhaus et al., 1979). Nonetheless, prolonged c.n.s. depression persisted for many days after discontinuation of diazepam. This could have been caused either by the underlying disease, or by persistence of diazepam and its metabolite after discontinuing administration. Since a precise relationship of plasma diazepam concentrations and clinical sedative effects has not been established, the cause of prolonged c.n.s. depression in this patient cannot be conclusively identified.

In the second patient, the washout half-lives of diazepam (43 h) and desmethyldiazepam (78 h) were within the range observed following single therapeutic doses in healthy individuals as described above. This was true despite the presence of advanced renal failure, which in previous studies has been shown not to impair the elimination of diazepam (Ochs et al., 1981b). Although simultaneous administration of cimetidine is known to impair diazepam clearance (Klotz and Riemann, 1980), it does not necessarily prolong diazepam half-life to a value exceeding the expected range.

The findings suggest that administration of high-dose i.v. diazepam leads to predictably large concentrations of diazepam and its major metabolite, desmethyldiazepam. There is no evidence of dose-dependent kinetics. However, the possibility of prolonged c.n.s. depression following termination of diazepam dosage should be considered.

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## REFERENCES

Allen, M. D., Greenblatt, D. J., Harmatz, J. S., and Shader, R. I. (1980). Desmethyldiazepam kinetics in the elderly after oral prazepam. *Clin. Pharmacol. Ther.*, 28, 196.

Dasta, J. F., Brier, K. L., Kidwell, G. A., Schonfeld, S. A., and Couri, D. (1981). Diazepam infusion in tetanus: correlation of drug levels with effect. *South. Med. J.*, 74, 278.

Greenblatt, D. J. (1978). Simultaneous gas chromatographic analysis for diazepam and its major metabolite, desmethyldiazepam, with use of double internal standardization. *Clin. Chem.*, 24, 1838.

——Allen, M. D., Harmatz, J. S., and Shader, R. I. (1980). Diazepam disposition determinants. *Clin. Pharmacol. Ther.*, 27, 301.

——Laughren, T. P., Allen, M. D., Harmatz, J. S., and Shader, R. I. (1981). Plasma diazepam and desmethyldiazepam concentrations during long-term diazepam therapy. *Br. J. Clin. Pharmacol.*, 11, 35.

——Ochs, H. R., and Lloyd, B. L. (1980). Entry of diazepam and its major metabolite into cerebrospinal fluid. *Psychopharmacol.*, 70, 89.

Kendall, M. J., and Clarke, S. W. (1972). Prolonged coma after tetanus. *Br. Med. J.*, 1, 354.

Klotz, U., Avant, G. R., Hoyumpa, A., Schenker, S., and Wilkinson, G. R. (1975). The effects of age and liver disease on the disposition and elimination of diazepam in adult man. *J. Clin. Invest.*, 55, 347.

Klotz, U., and Reimann, I. (1980). Delayed clearance of diazepam due to cimetidine. *N. Engl. J. Med.*, 302, 1012.

Mandelli, M., Tognoni, G., and Garattini, S. (1978). Clinical pharmacokinetics of diazepam. *Clin. Pharmacokinet.*, 3, 72.

Ochs, H. R., Greenblatt, D. J., Divoll, M., Abernethy, D. R., Feyerabend, H., and Dengler, H. J. (1981a). Diazepam kinetics in relation to age and sex. *Pharmacol.*, 23, 24.

——— Kaschell, H. J., Klehr, U., Divoll, M., and Abernethy, D. R. (1981b). Diazepam kinetics in patients with renal insufficiency or hyperthyroidism. *Br. J. Clin. Pharmacol.*, (in press).

Odusote, K. A., George, B. O., and Femi-Pearse, D. (1976). Favourable prognosis of prolonged coma associated with large doses of diazepam in severe tetanus. *Trop. Geogr. Med.*, 28, 194.

Ohnhaus, E. E., Park, B. K., Colombo, J. P., and Heizmann, P. (1979). The effect of enzyme induction on diazepam metabolism in man. *Br. J. Clin. Pharmacol.*, 8, 557.

Shader, R. I., Greenblatt, D. J., Ciraulo, D. A., Divoll, M., Harmatz, J. S., and Georgotas, A. (1981). Effect of age and sex on disposition of desmethyldiazepam formed from its precursor clorazepate. *Psychopharmacol.*, (in press).

## CINETIQUE DU DIAZEPAM INTRAVEINEUX A FORTES DOSES

### RESUME

La pharmacocinétique du diazepam i.v. à fortes doses a été étudiée chez deux patients de réanimation. Le premier patient a reçu des doses de diazepam atteignant 240 mg par jour pendant 21 jours et l'autre patient a reçu 60 mg/jour pendant 30 jours. Les concentrations plasmatiques de diazepam et de son principal métabolite, le déméthyldiazepam, étaient très élevées mais, malgré une pathologie associée très sévère et l'administration simultanée de plusieurs autres produits, les demi-vies d'élimination du diazepam et du déméthyldiazepam étaient du même ordre de grandeur que chez des individus bien portants. Chez le premier patient, les demi-vies d'élimination étaient même plutôt plus brèves que prévu, peut-être à cause d'une administration simultanée de phénobarbitone. Ainsi la cinétique du diazepam n'est apparemment pas modifiée par l'administration de fortes doses.

## KINETIK VON HOCHDOSIERTEM INTRAVENÖSEN DIAZEPAM

### ZUSAMMENFASSUNG

Die Pharmakokinetik von hochdosiertem intravenösen Diazepam wurde an zwei Patienten einer Intensivpflegeeinheit untersucht. Der erste Patient erhielt 21 Tage lang bis zu 240 mg pro Tag, während der zweite Patient 30 Tage lang 60 mg pro Tag bekam. Die Plasmakonzentrationen von Diazepam und seines Hauptmetaboliten, dem Desmethyldiazepam, waren sehr hoch, aber trotz der schweren Grundkrankheit und gleichzeitigen Verabreichung von mehreren anderen Medikamenten stimmten die Halbwertzeiten von Diazepam und von Desmethyldiazepam mit den bei gesunden Personen gefundenen Werten überein. Die Halbwertzeiten waren beim ersten Patienten, wenn überhaupt, kürzer als erwartet, was möglicherweise durch gleichzeitige Verabreichung von Phenobarbital bedingt war. Demnach ändert sich die Kinetik des Diazepam offensichtlich nicht bei Verabreichung hoher Dosen.

## CINETICA DEL DIAZEPAM EN ALTAS DOSIS I.V.

### SUMARIO

Se estudió la farmacocinética del diazepam en altas dosis i.v. administrado a dos pacientes de la unidad de cuidados intensivos. El primer paciente recibió hasta 240 mg de diazepam cada día durante 21 días mientras que el segundo recibía 60 mg diariamente por 30 días. Las concentraciones de diazepam y de su principal metabolito, el desmetildiazepam, eran muy altas pero, a pesar de la severa enfermedad subyacente y de la administración simultánea de varias otras substancias, las vidas medias del escurrimiento del diazepam y del desmetildiazepam fueron compatibles con las registradas en personas sanas. Las vidas medias del escurrimiento en el primer paciente fueron, acáso, más cortas de lo previsto, posiblemente a raíz de la administración simultánea de fenobarbitona. Entonces, la cinética del diazepam no se encontró alterada por la administración de altas dosis.

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# PLASMA CONCENTRATIONS OF LIGNOCAINE AND ITS METABOLITES DURING FIBREOPTIC BRONCHOSCOPY

D. A. JONES, A. MCBURNEY, P. J. STANLEY, C. TOVEY AND J. W. WARD

## SUMMARY

Lignocaine metabolites are known to have both antiarrhythmic and toxic effects. Large plasma concentrations of these metabolites have been reported following endotracheal instillation of lignocaine. We measured plasma lignocaine monoethylglycinexylidide (MEGX), and glycinexylidide (GX) concentrations for up to 4 h after fibreoptic bronchoscopy. The total dose of lignocaine required to suppress coughing varied between 230 mg and 364 mg. Small therapeutic lignocaine concentrations occurred transiently in nine of 19 patients after the bronchoscopy examination had finished. Only one patient achieved a plasma lignocaine concentration in the range of minor toxicity. Metabolite peaks occurred later and were of much smaller magnitude. They were unlikely to contribute to prophylaxis of cardiac arrhythmia or to toxicity. It would seem to be safe to use topical lignocaine in doses greater than the currently recommended maximum (200 mg) in conscious patients during fibreoptic bronchoscopy.

Although fibreoptic bronchoscopy is a relatively safe procedure, about one-third of the documented complications have been attributed to the use of the local anaesthetic agent (Credle, Smiddy and Elliott, 1974). Plasma concentrations of lignocaine have been reported during fibreoptic bronchoscopy (Patterson et al., 1975; Clausen et al., 1976), but the major metabolites monoethylglycinexylidide (MEGX) and glycinexylidide (GX) have received scant attention.

Both the antiarrhythmic activity and the toxicity of MEGX and GX are well recognized in animals, and these metabolites have been implicated in producing adverse effects in man in the presence of therapeutic concentrations of lignocaine (Strong et al., 1975). Smith (1976) reported that tracheal instillation of lignocaine resulted in plasma GX concentrations considerably greater than simultaneous lignocaine concentrations.

In this study we measured plasma concentrations of lignocaine, MEGX, and GX during routine fibreoptic bronchoscopy.

## PATIENTS AND METHODS

The first two patients booked for consecutive bronchoscopy lists over 3 months were invited to take part in the study. Nineteen gave informed consent and were examined bronchoscopically by one of two physicians (D.A.J., P.J.S.). Atropine 0.6 mg and papaveretum 7.5–15 mg according to body weight were given i.m. 30 min before the procedure. An "Atomist" hand nebulizer was used to deliver no more than six sprays of 4% lignocaine solution to each nostril and a similar number to the oropharynx. The nebulizer was weighed before and after use. A flexible bronchoscope (Olympus BF-B3) lubricated with a smear of 2% lignocaine gel was introduced via the nose and two injections of 4% lignocaine solution 1 ml were administered onto the vocal cords. Further 2-ml aliquots of 2% lignocaine solution were delivered to the proximal bronchial tree as required to suppress coughing, which was achieved within 10–15 min from the start of the procedure. Blood was withdrawn at intervals from an indwelling needle in a forearm vein.

Heparinized plasma was separated immediately and frozen at $-20$°C. Lignocaine concentrations were measured within 4 days, and MEGX and GX within 48 h, using the gas–liquid chromatographic technique of Adjepon-Yamoah and Prescott (1974). The method was modified as follows: lignocaine was extracted and assayed separately using 1 ml of plasma; the internal standard was phenacetin 100 μlitre of 40 $\mu g\ ml^{-1}$ solution for lignocaine, 10 μlitre for MEGX and GX; derivatization was at room temperature for 5 min using trifluoroacetic anhydride 10 μlitre. Gas chromatography conditions were: injector/detector temperature 250°C; oven temperature 210°C for lignocaine, 220°C for MEGX and

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GX; helium carrier gas, hydrogen, and air flow rates: 50, 100 and 4 ml min$^{-1}$ respectively; attenuation setting 32 for lignocaine, 16 for MEGX and GX.

Good separations were achieved between lignocaine, MEGX, GX and phenacetin. The assay was linear over the calibration ranges used (lignocaine 0–4.0 µg ml$^{-1}$, and MEGX and GX 0–0.4 µg ml$^{-1}$) and was reproducible. The coefficient of variation for replicate analyses ($n = 10$) for MEGX and GX 0.2 µg ml$^{-1}$ were 10.2% and 11.5% respectively. Plasma concentrations of MEGX and GX less than 0.05 µg ml$^{-1}$ were not detectable; above this concentration, measurement to 0.001 µg ml$^{-1}$ was possible. Percent recovery (mean ± SD) from plasma at the stated concentrations were: for lignocaine, 91.0 ± 6.3 at 0.5 µg ml$^{-1}$ and 82.5 ± 4.1 at 1.0 µg ml$^{-1}$; for MEGX 89.2 ± 10.4 at 0.2 µg ml$^{-1}$ and 82.2 ± 12.6 at 0.4 µg ml$^{-1}$; for GX 75.8 ± 16.9 at 0.2 µg ml$^{-1}$ and 68.5 ± 8.6 at 0.4 µg ml$^{-1}$. All calibration curves were prepared using drug-free plasma.

## RESULTS

Table I shows the total dose of lignocaine given, the maximum measured plasma lignocaine and MEGX concentrations, and the times when these were achieved in the 19 patients.

The maximum dose of lignocaine was 364 mg in patient 19. The maximum plasma lignocaine concentration was 3.34 µg ml$^{-1}$ in patient 10. This is within the therapeutic range recommended for suppression of arrhythmia (1.5–7.5 µg per ml of plasma (Aps et al., 1976)) and in total nine of the patients achieved concentrations within this range at times varying from 30 to 90 min from the start of nasal spraying. The mean peak plasma lignocaine concentration was 1.54 ± 0.15 µg ml$^{-1}$ (± SEM) and occurred between 30 and 90 min. Neither total lignocaine dose nor dose per kilogram body weight correlated well with the peak plasma concentrations of lignocaine ($r = 0.2$ and $r = 0.1$ respectively). In 13 patients it was possible to estimate the half-life of elimination ($T_{\frac{1}{2}}^{\beta}$) of lignocaine; this varied considerably between the patients with a mean of 159 ± 25 (SEM) min.

Plasma MEGX concentrations, measured in 11 patients, were much smaller than the lignocaine values, the maximum measured being 0.39 µg ml$^{-1}$. With one exception (patient 13, in whom the measured peaks occurred at the same time), MEGX peaks were later than lignocaine, and occurred between 60 and 210 min. The mean plasma peak MEGX was 0.25 ± 0.03 µg ml$^{-1}$ (± SEM).

Plasma GX concentrations were even smaller than

TABLE I. *Peak plasma concentrations of lignocaine and MEGX*

| Patient | Age (yr) | Weight (kg) | Diagnosis | Liver function tests | Total dose lignocaine (mg) | Peak lignocaine concn (µg ml$^{-1}$) | Time to peak lignocaine concn (min) | Peak MEGX concn (µg ml$^{-1}$) | Time to peak MEGX concn (min) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 57 | — | carcinoma | normal | 270 | 1.35 | 55 | — | — |
| 2 | 54 | 53 | carcinoma | normal | 230 | 1.62 | 30 | — | — |
| 3 | 66 | 88 | carcinoma | normal | 290 | 2.55 | 45 | — | — |
| 4 | 77 | 73 | carcinoma | normal | 230 | 1.01 | 45 | — | — |
| 5 | 71 | 68 | ? mesothelioma | normal | 250 | 2.29 | 30 | — | — |
| 6 | 73 | 51 | carcinoma | normal | 326 | 1.19 | 90 | — | — |
| 7 | 61 | 54 | carcinoma | ↑alk. phos. | 250 | 1.42 | 30 | — | — |
| 8 | 55 | 50 | carcinoma | normal | 230 | 1.82 | 90 | — | — |
| 9 | 54 | 60 | haemoptysis | — | 352 | 1.48 | 30 | 0.168 | 210 |
| 10 | 58 | 67 | carcinoma | ↑alk. phos. and gamma GT | 310 | 3.34 | 90 | 0.250 | 150 |
| 11 | 48 | 65 | haemoptysis | — | 284 | 0.57 | 30 | 0.181 | 210 |
| 12 | 69 | 62 | carcinoma | normal | 228 | 1.67 | 45 | 0.340 | 210 |
| 13 | 63 | — | haemoptysis | normal | 310 | 0.95 | 60 | 0.350 | 60 |
| 14 | 28 | 70 | carcinoma | normal | 350 | 2.04 | 45 | 0.390 | 60 |
| 15 | 65 | 80 | carcinoma | normal | 296 | 0.97 | 45 | 0.389 | 90 |
| 16 | 64 | 69 | bronchitis | normal | 272 | 1.41 | 35 | 0.166 | 150 |
| 17 | 49 | 70 | lung fibrosis | normal | 360 | 0.80 | 45 | 0.136 | 210 |
| 18 | 50 | 79 | carcinoma | normal | 244 | 1.40 | 30 | 0.230 | 120 |
| 19 | 59 | 54 | tuberculosis | ↑alk. phos. and gamma GT | 364 | 1.46 | 45 | 0.129 | 90 |

those of MEGX, and were undetectable or present in only trace amounts (that is up to 0.05 μg $ml^{-1}$) up to 4 h in six of the 11 patients in whom measurement was attempted. The plasma concentration *v.* time profiles for lignocaine, MEGX and GX are shown in figure 1.

Lignocaine $T_{\frac{1}{2}}^{\beta}$ correlated well with time to peak plasma MEGX ($r = 0.8$). Thus, patients with short lignocaine half-lives showed early MEGX peaks. In two such patients (14 and 15) early peaks allowed $T_{\frac{1}{2}}^{\beta}$ for MEGX to be estimated at 134 and 129 min respectively, and in patient 15, $T_{\frac{1}{2}}^{\beta}$ for GX was 389 min. These values are in accord with previously published data (Adjepon-Yamoah and Prescott, 1973; Strong, Parker and Atkinson, 1973; Strong et al., 1975).

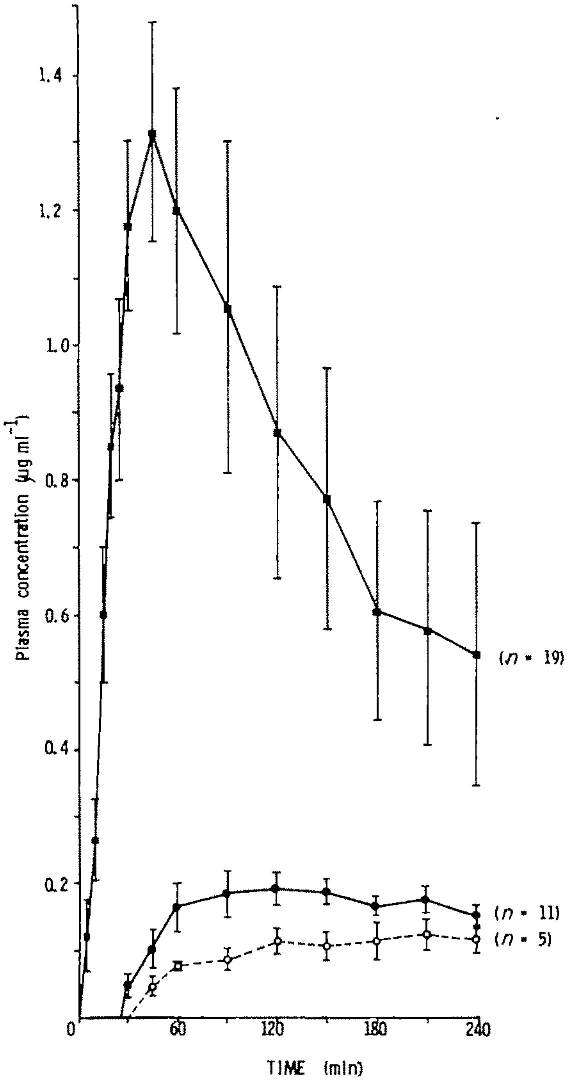

FIG. 1. Mean plasma concentrations (±SEM) *v.* time profiles for lignocaine, MEGX and GX. ■ = lignocaine concentration; ● = MEGX concentration; ○ = GX concentration; *n* = number of patients studied.

## DISCUSSION

The recommended maximum dose of lignocaine for infiltration anaesthesia is 200 mg (Pharmaceutical Codex, 1979). Similarly, the manufacturers recommend the use of no more than 200 mg during fibreoptic bronchoscopy (Data Sheet Compendium, 1980–81), although a study of the literature lends no supportive evidence for this upper limit. As is the common practice in most centres, the patients in our study were given sufficient lignocaine to suppress coughing without any fixed upper limit in mind, and all required more than 200 mg for adequate anaesthesia. There were no complaints of adverse effects, and the greatest concentration of lignocaine was 3.34 μg $ml^{-1}$ in a patient known to have impaired liver function (table I, patient 10). Objective adverse effects such as muscular irritability, convulsions and coma may occur at venous blood concentrations of 6–10 μg $ml^{-1}$, and subjective central nervous system effects such as drowsiness and dizziness at concentrations of 3–5 μg $ml^{-1}$ (Gianelly et al., 1967, Benowitz, 1974).

It is known that not all the lignocaine given during bronchoscopy reaches the systemic circulation. In addition to losses from initial coughing (Scott et al., 1976), or aspiration via the bronchoscope (Bartlett et al., 1976), some is swallowed and oral lignocaine has a bioavailability of only about 35% because of "first pass" hepatic metabolism (Boyes et al., 1971). In man, the main urinary metabolite is 4 hydroxy 2,6 dimethyl-aniline, but the compounds found in the blood known to be associated with pharmacological effects are MEGX and GX (Keenaghan and Boyes, 1972; Tucker, 1975). In rodents, MEGX is as toxic to the central nervous system as lignocaine (Smith and Duce, 1971) though GX is less so (Blumer, Strong and Atkinson, 1973), being devoid of convulsant activity and, in man, producing only minimal impairment of mental function at plasma concentrations up to 4 μg $ml^{-1}$ (Strong et al., 1975).

In all our patients, lignocaine concentrations were in excess of the concentrations of both MEGX and GX, an observation which is in marked contrast to two previous reports of high circulating metabolite concentrations following endotracheal lignocaine administration. Thus Cohn, Smith and Sievenpiper (1972) recorded plasma metabolite concentrations at least four times that of circulating lignocaine, and Smith (1976) reported serum GX peaks in excess of $6\,\mu g\,ml^{-1}$ in the presence of lignocaine concentrations of less than $1\,\mu g\,ml^{-1}$.

Nine of our patients achieved lignocaine concentrations in the lower range for suppression of arrhythmias, mostly at times well after completion of the examination. These concentrations were present only for a short period of time. Elguindi and others (1979) using doses much greater than in our series (580–1330 mg; mean 777 mg), reported that lignocaine decreased the frequency of major arrhythmias during fibreoptic bronchoscopy, but at the expense of producing dizziness in some patients. Under the conditions of our study, peak plasma concentration did not correlate with either the total dose of lignocaine given or the dose per kilogram body weight, so that it is not possible to predict which patients might be at risk of developing symptoms during or after the examination. It is of interest to compare this situation with lignocaine given by subcutaneous infiltration, when peak plasma concentration correlates reasonably well with the total dose administered ($r = 0.82$), but not with the dose per kilogram body weight (Scott et al., 1972).

Peak concentrations of lignocaine occur after bronchoscopy in the majority, just as observation is becoming less intensive. Although we conclude that lignocaine in doses greater than 200 mg sufficient to suppress coughing is safe, our advice to patients and nursing staff now includes the possibility that minor subjective symptoms may occur for the first time after the procedure has finished. There would appear to be little danger of intoxication from metabolites.

## REFERENCES

Adjepon-Yamoah, K. K., and Prescott, L. F. (1973). Lignocaine metabolism in man. *Br. J. Pharmacol.*, 47, 672.

—— —— (1974). Gas–liquid chromatographic estimation of lignocaine, ethylglycylxylidide, glycylxylidide and 4-hydroxyxylidide in plasma and urine. *J. Pharm. Pharmacol.*, 26, 889.

Aps, C., Bell, J. A., Jenkins, B. S., Poole-Wilson, P. A., and Reynolds, F. (1976). Logical approach to lignocaine therapy. *Br. Med. J.*, 1, 13.

Bartlett, J. G., Alexander, J., Mayhew, J., Sullivan-Sigler, N., and Gorbach, S. L. (1976). Should fibreoptic bronchoscopy aspirates be cultured? *Am. Rev. Respir. Dis.*, 114, 73.

Benowitz, N. L. (1974). Clinical applications of the pharmocokinetics of lidocaine; in *Cardiovascular Drug Therapy* (ed. K. Melmon), p. 77. Philadelphia: Davis.

Blumer, J., Strong, J. M., and Atkinson, A. J. jr (1973). The convulsant potency of lidocaine and its N-dealkylated metabolites. *J. Pharm. Exp. Ther.*, 186, 31.

Boyes, R. N., Scott, D. B., Jebson, P. J., Goodman, M. J., and Julian, D. G. (1971). Pharmacokinetics of lidocaine in man. *Clin. Pharmacol. Ther.*, 12, 105.

Clausen, J. L., Hill, R. N., Liewen, M. B., and Catlin, D. H. (1976). Arterial and venous lidocaine levels during fibreoptic bronchoscopy. *Am. Rev. Respir. Dis.*, 113/4, 129.

Cohn, M. L., Smith, R. B., and Sievenpiper, T. (1972). Concentrations of lidocaine and its metabolites in the blood after endotracheal administration. *Exerpta Medica Fifth World Congress of Anaesthesiologists*, 261, 118.

Credle, W. F. jr, Smiddy, J. F., and Elliott, R. C. (1974). Complications of fiberoptic bronchoscopy. *Am. Rev. Respir. Dis.*, 109, 67.

*Data Sheet Compendium* (1980–81), p. 83. London: Datapharm Publications Ltd.

Elguindi, A. S., Harrison, G. N., Abdulla, A. M., Chaudhary, B. A., Vallner, J. J., Kolbeck, R. C., and Speir, W. A. jr (1979). Cardiac rhythm disturbances during fiberoptic bronchoscopy; a prospective study. *J. Thorac. Cardiovasc. Surg.*, 77, 557.

Gianelly, R., Von der Groeben, J. O., Spivack, A. P., and Harrison, D. C. (1967). Effect of lidocaine on ventricular arrhythmias in patients with coronary heart disease. *N. Engl. J. Med.*, 277, 1215.

Keenaghan, J. B., and Boyes, R. N. (1972). The tissue distribution, metabolism and excretion of lidocaine in rats, guinea pigs, dogs and man. *J. Pharmacol. Exp. Ther.*, 180, 454.

Patterson, J. R., Blaschke, T. F., Kellog Hunt, K. jr and Meffin, P. J. (1975). Lidocaine blood concentrations during fibreoptic bronchoscopy. *Am. Rev. Respir. Dis.*, 112, 53.

*Pharmaceutical Codex* (1979), 11th Edn, p. 493. London: The Pharmaceutical Press.

Scott, D. B., Jebson, P. J. R., Braid, D. P., Ortengren, B., and Frisch, P. (1972). Factors affecting plasma levels of lignocaine and prilocaine. *Br. J. Anaesth.*, 44, 1040.

—— Littlewood, D. G., Covino, B. G., and Drummond, G. B. (1976). Plasma lignocaine concentrations following endotracheal spraying with an aerosol. *Br. J. Anaesth.*, 48, 899.

Smith, E. R., and Duce, B. R. (1971). The acute antiarrhythmic and toxic effects in mice and dogs of 2-ethylamino-2′, 6′-acetoxylidine (1–86), a metabolite of lidocaine. *J. Pharmacol. Exp. Ther.*, 179, 580.

Smith, R. B. (1976). Uptake of lidocaine from the trachea. *Anesthesiology*, 44, 269.

Strong, J. M., Mayfield, D. E., Atkinson, A. J. jr, Burris, B. C., Raymon, F., and Webster, L. T. jr (1975). Pharmacological activity, metabolism, and pharmacokinetics of glycinexylidide. *Clin. Pharm. Ther.*, 17, 184.

—— Parker, M., and Atkinson, A. J. jr (1973). Identification of glycinexylidide in patients treated with intravenous lidocaine. *Clin. Pharm. Ther.*, 14, 67.

Tucker, G. T. (1975). Biotransformation and toxicity of local anaesthetics. *Acta Anaesthesiol. Belg.* (Suppl.), 23, 123.

## CONCENTRATIONS PLASMATIQUES DE LIGNOCAINE ET DE SES METABOLITES AU COURS DE LA FIBROSCOPIE BRONCHIQUE

### RESUME

Les métabolites de la lignocaïne sont connus à la fois pour leurs propriétés antiarrythmiques et pour leurs effets toxiques. On a rapporté l'existence de fortes concentrations de ces métabolites après instillation endotrachéale de lignocaïne. Nous avons mesuré les concentrations plasmatiques de lignocaïne, de monoéthylglycinexylidide (MEGX) et de glycinexylidide (GX) au cours des quatre heures suivant une fibroscopie bronchique. La dose totale de lignocaïne nécessaire à la suppression de la toux variait de 230 à 364 mg. Chez 9 patients sur 19, des concentrations thérapeutiques faibles de lignocaïne ont été observées transitoirement après la fin de la fibroscopie. Il n'y a que chez un patient que les concentrations plasmatiques de lignocaïne ont atteint la zone de toxicité mineure. Les pics de métabolites étaient plus tardifs et de bien moindre amplitude. Il y a peu chance qu'ils aient pu contribuer à la prophylaxie de troubles du rythme cardiaque ou à une quelconque toxicité. Il semblerait que l'on puisse en toute sécurité utiliser la lignocaïne en application locale à des doses supérieures au maximum habituellement recommandé (200 mg) chez des sujets conscients au cours de fibroscopies bronchiques.

## PLASMAKONZENTRATIONEN VON LIDOCAIN UND SEINER METABOLITE WÄHREND DER FIBEROPTIK-BRONCHOSKOPIE

### ZUSAMMENFASSUNG

Bekanntlich besitzen Lidocain-Metabolite sowohl antiarrhythmische als auch toxische Wirkungen. Es wurde berichtet, daβ nach endotrachealer Verabreichung von Lidocain hohe Plasmakonzentrationen dieser Metabolite auftreten. Wir bestimmten das Plasmalidocain, das Monoäthylglycinhexylidid (MEGX) und die Glycinhexylidid-konzentrationen (GX) 4 Stunden nach Fiberoptik-Bronchoskopie. Die Gesamtdosis an Lidocain, die notwendig war, um den Hustenreiz zu unterdrücken, schwankte zwischen 230 mg und 364 mg. Niedrige therapeutische Lidocain-Konzentrationen waren vorübergehend bei neun von 19 Patienten nach Ende der Bronchoskopie nachweisbar. Nur bei einem Patienten trat eine leicht toxische Lidocain-Konzentration auf. Die höchsten Werte der Metabolite traten später auf, waren aber wesentlich kleiner. Es ist unwahrscheinlich, daβ diese zur Prophylaxe von Herzarrhythmien beitragen oder toxische Wirkungen hervorrufen. Es scheint ungefährlich zu sein, lokale Lidocaindosen zu verwenden, die gröβer als die derzeit empfohlene Höchstdosis (200 mg) für wache Patienten bei der Endoskopie mit Fiberoptik ist.

## CONCENTRACIONES DE LIGNOCAINA Y DE SUS METABOLITOS EN EL PLASMA DURANTE LA BRONCOSCOPIA CON FIBRA OPTICA

### SUMARIO

Se sabe que los metabolites de lignocaína ejercen efectos tóxicos y antiarrítmicos. Se ha notificado de la presencia de grandes concentraciones de estos metabolitos en el plasma a raiz de la instalación endotraqueal de lignocaína. Medimos las concentraciones de lignocaína, monoetilglicenexilidida (MEGX) y glicenexilidida (GX) en el plasma por espacio de 4 horas después de la broncoscopia con fibra óptica. La dosis total de lignocaína necesaria para suprimir la tos varió entre 230 mg y 364 mg. En 9 de los 19 pacientes aparecieron pequeñas concentraciones de lignocaína terapéutica con carácter temporal después de haber terminado la broncoscopia. Sólo uno de los pacientes llegó a alcanzar una concentración de lignocaína en el plasma que caía dentro de la gama de la toxicidad menor. Las crestas correspondientes a los metabolitos tuvieron lugar con posterioridad y fueron de una magnitud mucho menor. No se considera probable que estos contribuyeran a la arrítmia, profilaxis o la toxicidad. El uso de lignocaína topical parece ser suguro en dosis superiores al máximo actualmente recomendado (200 mg) en pacientes conscientes sometidos a broncoscopia con fibra óptica.

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# IMMUNOLOGICAL ASPECTS OF ADVERSE REACTIONS TO ALTHESIN

S. G. RADFORD, J. A. LOCKYER AND P. J. SIMPSON

## SUMMARY

Sequential plasma samples from 30 patients showing clinical signs of hypersensitivity to Althesin were investigated to determine if a specific immune response to the drug was present (as measured by classical complement pathway activation) or if a non-antibody-dependent alternative complement pathway activation was taking place. The patients were classified as those reacting on first exposure to Althesin and those who reacted adversely only on a second exposure. The alternative complement pathway, but not the classical pathway, was activated in five of the 13 first-time reactors, while in the remaining eight no complement activation was detected. In contrast, classical complement pathway activation was demonstrated in the blood samples of all 17 patients reacting on repeat exposure. Severe reactions occurred in nine of the 17 previously exposed patients compared with only one of the 13 reacting on first exposure to Althesin.

The reported frequency of hypersensitivity reactions to the i.v. anaesthetic agent Althesin (alphaxalone/alphadolone acetate in Cremophor EL) has varied from 1 in 930 (Evans and Keogh, 1977) to 1 in 433 (Beamish, 1979) and is considerably greater than for barbiturates (Evans and Keogh, 1977; Whitwam, 1978). Although adverse responses to Althesin may follow a first or subsequent exposure, the relative frequency of reactions in these two situations is unknown. Since it is unlikely that both reactions are mediated in the same way, we have investigated 30 cases of apparent hypersensitivity to Althesin for possible immunological involvement and report the clinical and laboratory findings.

The clinical signs are those typical of an anaphylactic reaction produced by generalized histamine release which may occur immunologically either by IgE-mediated immediate hypersensitivity not involving complement, or by activation of the complement cascade. Two separate pathways exist for complement activation: the classical pathway, initiated by an antigen–antibody interaction in which the antibody involved is IgG or IgM, and the alternative pathway in which no antibody is involved. Both IgE- and classical pathway-mediated hypersensitivity responses are dependent upon previous exposure to the antigen. Various conflicting reports have suggested that Althesin reactions involve either IgE (Watkins, 1979; Fisher, 1980), classical (Watkins, Allen and Milford Ward, 1978) or alternative complement pathway activation (Watkins, Clarke et al., 1976; Watkins, Udnoon et al., 1976). A direct non-immunologically-mediated effect of the drug on mast cells, releasing histamine, has also been suggested (Watkins, Clark et al., 1976; Watkins, 1979).

## METHODS

### *Clinical observations*

The 30 patients reported represent the total number referred to us in whom Althesin alone could be held responsible for their hypersensitivity reactions. A number of other patients to whom Althesin was administered simultaneously with another drug known to cause hypersensitivity, for example alcuronium chloride (Fisher, Hallowes and Wilson, 1978), have been excluded. Clinical signs of hypersensitivity varied widely (table I), although no reaction was fatal. The severity of the response was assessed clinically by the degree of cardiovascular collapse, a severe reaction being classified as one in which the systolic arterial pressure decreased to less than 60 mm Hg in conjunction with other symptoms of anaphylaxis.

In every patient, following resuscitative treatment, anaesthesia and surgery proceeded uneventfully. The medical histories of the patients were re-examined and none in this study was found to have any known immunological or haematological disease. Patient 22, however, was undergoing radiotherapy for uterine cervical neoplasm, and pa-

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TABLE I. *Clinical signs of hypersensitivity*

| Symptom | 1st-time reactors (%) | 2nd-time reactors (%) |
|---|---|---|
| Rash | 15 | 18 |
| Flush | 55 | 53 |
| Oedema | 38 | 29 |
| Tachycardia | 23 | 24 |
| Cough | 23 | 42 |
| Bronchospasm | 31 | 53 |
| Cyanosis | 8 | 42 |
| Hypotension/cardiovascular collapse | 8 | 70 |

tient 13 was suffering from an axillary abscess. We are unable to determine if these conditions affected their immune status.

### *Blood samples*

Sequential samples of venous blood were collected into specially prepared bottles containing di-potassium ethylene diamine tetracetic acid (EDTA) 1 mg ml$^{-1}$ at the time of reaction and at increasing intervals over the next 24 h. The plasma from these samples was separated as quickly as possible and deep frozen if analysis was not to be performed immediately.

Two-dimensional immunoelectrophoresis was used to identify the breakdown products of the C3 complement component, based upon a modification (Versey, 1973) of the Laurell technique (Laurell, 1965) (fig. 1). C3 and C4 concentrations were measured by rocket immunoelectrophoresis (Axleson, Kroll and Weeke, 1973) using, respectively, anti-C3 prepared at the Regional Blood Transfusion Centre, Bristol and commercially available anti-C4 (Dako, Mercia Brocades) (fig. 2). C1 esterase inhibitor was also measured by this technique using commercial antibody (Hoechst Pharmaceuticals, Hounslow).

## RESULTS

The 30 patients were subdivided into those suffering a hypersensitivity reaction on first exposure to Althesin (table II) and those who had previously received the drug (table III). Thirteen patients developed clinical signs of anaphylaxis on first exposure to Althesin. No complement conversion was found in the samples from eight of these patients, none of whom suffered a severe reaction. The decrease in C3 concentration in the plasma of patient 8 occurred in the absence of C3 conversion which would have indicated immunological involvement. The remaining five all demonstrated C3 conversion, without accompanying reduction in C4 concentration. Only one of these five patients suffered a severe reaction.

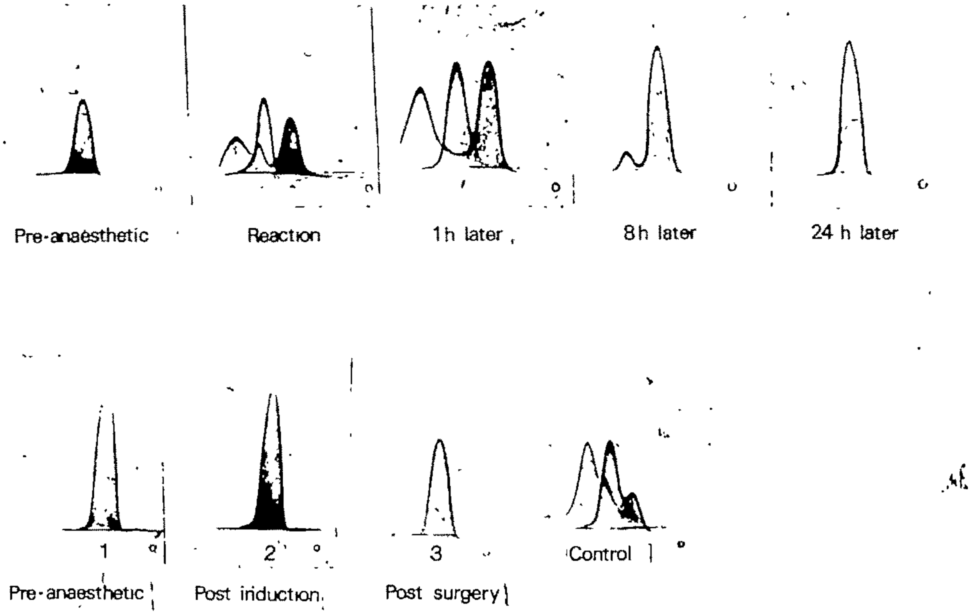

FIG. 1. Two-dimensional immunoelectrophoresis. The top row shows a typical "positive" reaction pattern; the converted C3 peaks, C3c and C3d are seen to the left of the native C3 peak. The sample taken at the time of reaction shows 60% conversion. The lower row shows a typical "negative" reaction pattern.

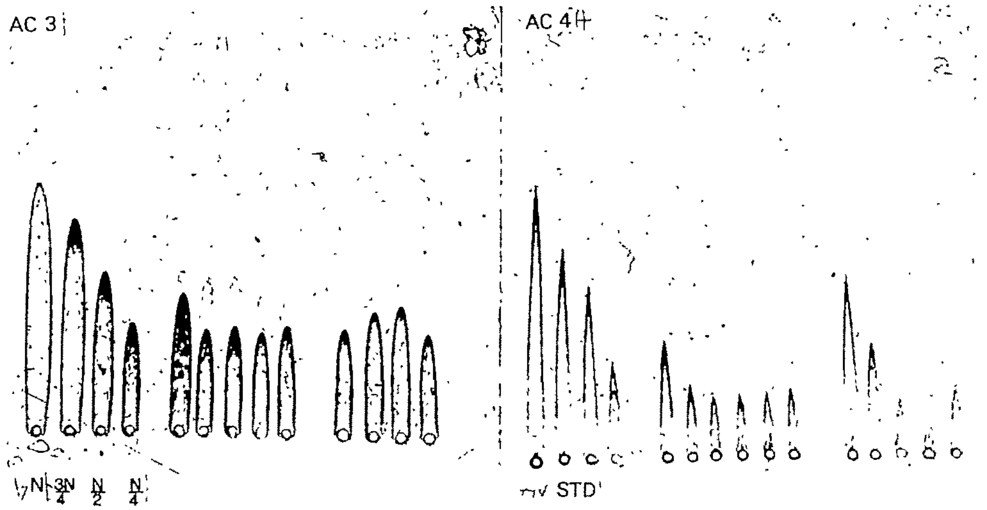

FIG. 2. The two plates illustrate rocket immunoelectrophoresis for the measurement of C3 and C4 concentrations. The plate on the right shows the decrease in C4 concentration in theplasma of two patients following an adverse reaction. The first sample in each case was taken before induction.

The results of the 17 patients who had previously been exposed to Althesin are shown in table III. C3 conversion occurred in every case. Of the 14 in whom C4 was measured, 12 showed marked C4 consumption ranging from 18% to 93%, while in two the concentrations were unchanged. The dilutional effect of i.v. fluid therapy was considered in relation to C4 reduction, but was felt unlikely to be responsible for changes of this magnitude. In contrast to the patients reacting on first exposure to the drug, nine of the 17 re-exposed patients suffered a severe clinical reaction.

C1 esterase inhibitor concentrations were measured in all patients to exclude anyone with pre-existing reduced concentrations characteristic of hereditary angioneurotic oedema. The apparently large concentrations found in some patients, while having no bearing on the immune reaction, probably reflect tissue trauma which inevitably produces increased concentrations of this acute phase protein.

TABLE II. *Results from 13 patients who developed clinical signs of anaphylaxis on first exposure to Althesin*

| Patient No. | Age (yr) | Sex | C3 conversion | C3 concn | C4 concn | Clinical severity |
|---|---|---|---|---|---|---|
| 1 | 32 | F | – | unchanged | unchanged | mild |
| 2 | 16 | F | – | unchanged | unchanged | mild |
| 3 | 17 | F | – | not measured | not measured | mild |
| 4 | 18 | F | – | unchanged | unchanged | mild |
| 5 | 23 | F | – | unchanged | unchanged | mild |
| 6 | 25 | F | – | unchanged | unchanged | mild |
| 7 | 66 | F | – | unchanged | unchanged | mild |
| 8 | 45 | F | – | decreased | unchanged | mild |
| 9 | 41 | F | + | decreased | unchanged | severe |
| 10 | 36 | M | + | unchanged | unchanged | mild |
| 11 | 34 | F | + | unchanged | unchanged | mild |
| 12 | 32 | F | + | decreased | unchanged | mild |
| 13 | 26 | F | + | unchanged | unchanged | mild |

## DISCUSSION

The complement system is a series of nine plasma proteins, activated as a cascade the ultimate effect of which is to produce cell lysis (fig. 3). Classical activation of this system following a type II or III hypersensitivity reaction as described by Gell, Coombs and Lachmann (1975) involves the C1, 4, 2 sequence. In the alternative pathway, C3 conversion may be initiated by a number of substances such as bacterial polysaccharides, virally infected cells and various toxins. This activation does not involve

TABLE III. *Results from 17 patients who had previously been exposed to Athesin*

| Patient No. | Age (yr) | Sex | C3 conversion | C3 concn | C4 concn | Clinical severity | Previous exposure |
|---|---|---|---|---|---|---|---|
| 14 | 17 | M | + | unchanged | decreased 25% | mild | 19 days |
| 15 | 21 | F | + | decreased 32% | decreased 70% | severe | 14 days |
| 16 | 24 | F | + | decreased 42% | decreased 18% | severe | 11 months |
| 17 | 8 | M | + | decreased 34% | decreased 70% | severe | 10 days |
| 18 | 37 | M | + | decreased 31% | decreased 75% | severe | 14 days |
| 19 | 19 | M | + | decreased 75% | decreased 86% | severe | 24 days |
| 20 | 62 | M | + | decreased 46% | decreased 39% | mild | 2 years |
| 21 | 21 | F | + | decreased 24% | decreased 75% | mild | 19 months |
| 22 | 20 | F | + | decreased 41% | decreased 66% | severe | 2 months |
| 23 | 11 | M | + | unchanged | unchanged | mild | 1 day |
| 24 | 27 | F | + | unchanged | unchanged | mild | 6 months |
| 25 | 28 | F | + | decreased 80% | decreased 93% | severe | 2 weeks |
| 26 | 9 | M | + | decreased 36% | decreased 75% | mild | 1 week |
| 27 | 44 | F | + | not measured | not measured | severe | 7 weeks |
| 28 | 18 | F | + | not measured | not measured | mild | 9 months |
| 29 | 23 | F | + | not measured | not measured | severe | 4 months |
| 30 | 16 | M | + | decreased 42% | decreased 50% | mild | 10 days |

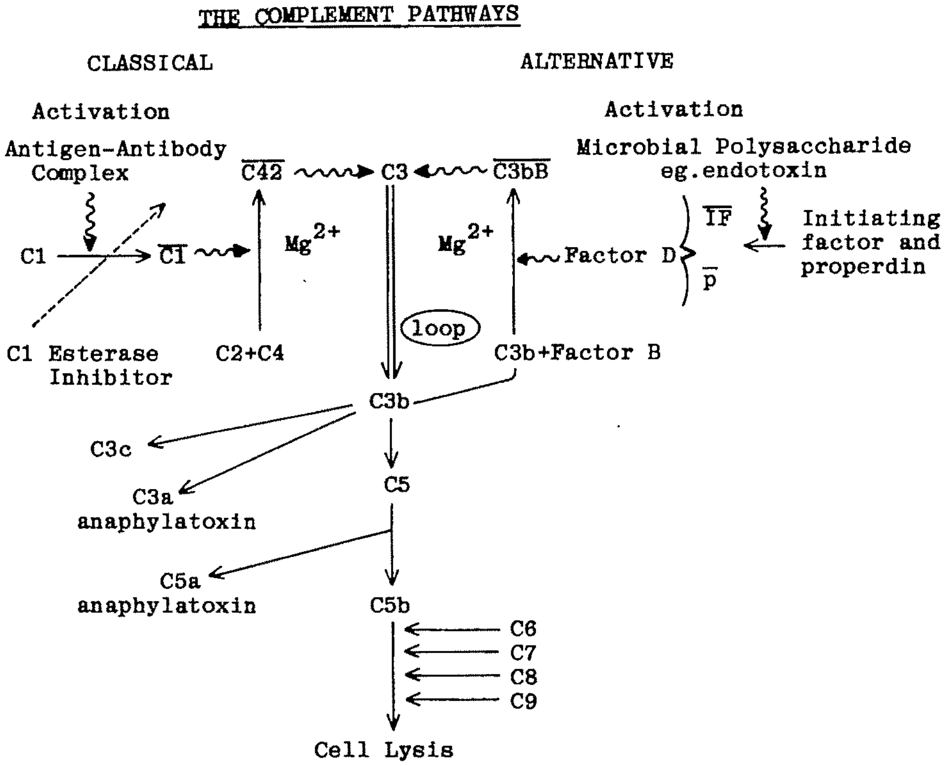

FIG. 3. Routes of activation of the complement pathways leading ultimately to cell lysis. Complement fractions which have been activated are represented thus: C1.

antibody and therefore does not require previous sensitization.

While C3 activation is common to both classical and alternative pathways, C4 is involved only in the classical pathway. Histamine release following activation of the complement cascade is produced by the action of anaphylatoxins (C3a and C5a) on mast cells. The final common pathway of both routes of activation is C5–9.

In contrast to previous reports (Watkins, Allen and Milford Ward, 1978; Watkins, 1979; Fisher, 1980) which suggest various mechanisms responsible for hypersensitivity reactions to Althesin, our results demonstrate a distinct difference in complement involvement between those patients reacting on first exposure and those who have been previously sensitized to the drug. Isolated conversion of the C3 complement component, as seen in all of the five immunologically-mediated first time reactors (table II) implies that hypersensitivity has occurred by direct activation of the alternative pathway. It is not clear which mechanism was responsible in the eight remaining first-time reactors in whom no immunological involvement was seen. The involvement of both C3 and C4 observed in the patients reacting on re-exposure to Althesin is diagnostic of classical complement pathway activation typically occurring following a Type II or III hypersensitivity reaction (Gell, Coombs and Lachmann, 1975) and implies immune recognition.

The consistent activation of the classical complement pathway in all our patients reacting on re-exposure to Althesin would not have occurred if the antibody involved was IgE, because IgE does not bind complement. The role of IgE-mediated hypersensitivity in Althesin reactions has been described by Fisher (1980), who claimed that the majority of his patients show a positive response to intradermal skin testing following adverse reactions.

Since our results show that reactions following re-exposure to Althesin mimic Type II or III hypersensitivity reactions, the recommendation (Dinmore, 1979) that patients should be given an i.v. test dose must be viewed with extreme caution. Minute quantities of antigen are sufficient to precipitate anaphylaxis in a previously sensitized patient. Furthermore, we would not agree with the suggestion (Dinmore, 1979) that reactions on first exposure to Althesin are dose-related in intensity. One of our patients (No. 10) reacted on first exposure to a 0.5-ml test dose of the drug.

In conclusion, we believe that confirmation of a true hypersensitivity reaction to Althesin requires not only a clinical history of anaphylaxis, but also immunological evidence of complement activation. A distinct difference exists between the immunological mechanisms involved in reactions following first and subsequent exposure to Althesin. We believe that the frequency of severe reaction would be considerably reduced by avoiding re-exposure to the drug.

## ACKNOWLEDGEMENTS

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## REFERENCES

Axelson, N. H., Kroll, J., and Weeke, B. (1973). *A Manual of Quantitative Immunoelectrophoresis*, 1st edn, p. 36. Oslo: Universitetsforlaget.

Beamish, D. (1979). Adverse response to Althesin. *Anaesthesia*, **34**, 683.

Dinmore, P. (1979). Althesin sensitivity testing. *Anaesthesia*, **34**, 374.

Evans, J. M., and Keogh, J. A. M. (1977). Adverse reactions to intravenous anaesthetic induction agents. *Br. Med. J.*, **2**, 735.

Fisher, M. McD. (1980). Reaginic antibodies to drugs used in anesthesia. *Anesthesiology*, **52**, 318.

—— Hallowes, R. C., and Wilson, R. M. (1978). Anaphylaxis to alcuronium. *Anaesth. Intens. Care*, **6**, 125.

Gell, P. G. H., Coombs, R. R. A., and Lachmann, P. (1975). *Clinical Aspects of Immunology*, 3rd edn, p. 871. Oxford: Blackwell Scientific Publications.

Laurell, C. B. (1965). Antigen–antibody crossed electrophoresis. *Analyt. Biochem.*, **10**, 358.

Versey, J. M. B. (1973). Automated two-dimensional immunoelectrophoresis and its application to the analysis of C3 and C4 in rheumatoid arthritis and systemic lupus erythematosus (SLE). *Ann. Clin. Biochem.*, **10**, 100.

Watkins, J. (1979). Anaphylactoid reactions to i.v. substances. *Br. J. Anaesth.*, **51**, 51.

—— Allen, R., and Milford Ward, A. (1978). Adverse response to alphadolone/alphaxalone. *Lancet*, **2**, 736.

—— Clark, A., Appleyard, T. N., and Padfield, A. (1976). Immune-mediated reactions to Althesin (alphaxalone). *Br. J. Anaesth.*, **48**, 881.

—— Udnoon, S., Appleyard, T. N., and Thornton, J. A. (1976). Identification and quantitation of hypersensitivity reactions to intravenous anaesthetic agents. *Br. J. Anaesth.*, **48**, 457.

Whitwam, J. G. (1978). Adverse reactions to i.v. induction agents. *Br. J. Anaesth.*, **50**, 677.

## ASPECTS IMMUNOLOGIQUES DES EFFETS SECONDAIRES NEFASTES A L'ALTHESIN

### RESUME

Des séquences d'échantillons plasmatiques venant de 30 patients ayant des signes cliniques d'hypersensibilité à l'Althésin ont été étudiées pour rechercher s'il y avait une réponse immune spécifique au produit (mesurée par l'activation de la voie classique du complément) ou s'il y avait une activation de la voie alterne du complément, ne dépendant pas d'un anticorps. Les patients ont été classés en séparant ceux qui réagissaient à la première exposition à l'Althésin de ceux qui ne réagissaient qu'à une seconde exposition. Chez cinq des 13 individus réagissant dès la première fois, la voie alterne du complément était activée, mais pas la voie classique, tandis que chez les huit autres on ne retrouvait pas d'activation du complément. A l'inverse, l'activation de la voie classique du complément a été mise en évidence dans les échantillons sanguins de tous les 17 patients réagissant à des expositions répétées. Des réactions sévères ont été retrouvées chez neuf des 17 patients ayant déjà été exposés et seulement chez un des 13 patients réagissant à la première exposition à l'Althésin.

## IMMUNOLOGISCHE ASPEKTE VON PARADOXEN REAKTIONEN AUF ALTHESIN

### ZUSAMMENFASSUNG

Plasmaproben von 30 Patienten, die klinische Zeichen einer Überempfindlichkeit auf Althesin gezeigt hatten, wurden in einer bestimmten Reihenfolge entnommen. Diese wurden untersucht, um herauszufinden, ob eine spezifische Immunantwort auf das Mittel vorhanden war (wie sie mit der klassischen Komplementaktivierung gemessen wird), oder ob eine nicht-Antikörper-vermittelte Komplementaktivierung stattfand. Die Patienten wurden klassifiziert als solche, die bei der ersten Verabreichung von Althesin und solche, die beim Zweitenmal reagiert haen. Die alternative Komplementaktivierung, aber nicht die klassische, fand bei 5 von 13 Patienten statt, die auf die erste Gabe reagiert hatten, während bei den übrigen 8 Patienten keine Komplementaktivierung nachgewiesen werden konnte. Im Gegensatz dazu zeigte sich die klassische Komplementaktivierung in den Blutproben bei allen 17 Patienten, die bei wiederholter Exposition reagiert hatten. Ernste Reaktionen kamen bei 9 von den 17 schon früher exponierten Patienten vor, verglichen mit nur einer Reaktion bei den 13 Patienten, die bei der ersten Exposition auf Althesin reagiert hatten.

## ASPECTOS INMUNOLOGICOS DE LAS REACCIONES ADVERSAS A LA ALTESINA

### SUMARIO

Se investigó muestras secuenciales de plasma de 30 pacientes que daban señales clínicas de hipersensibilidad a la altesina con el objeto de determinar si existía una respuesta específica de inmunidad a dicha substancia (medida por la activación clásica de la senda del complemento) o si ocurría una activación de la senda del complemento alternativa nodependiente de los anticuerpos. Se repartieron a los pacientes en dos clases: los que tuvieron una reacción después de la primera exposición a la altesina y los que reaccionaron de manera adversa solamente después de la segunda exposición. En cinco de los que reaccionaron a la primera exposición (13), se activó la senda del complemento alternativo, mas no se activó a la senda clásica, mientras que en los últimos ocho pacientes, no se observó alguna activación del complemento. En contraste, se observó una activación de la senda del complemento clásico en las muestras de sangre de todos los 17 pacientes cuya reacción se produjo después de una exposición reiterada. Tuvieron lugar severas reacciones en nueve de los 17 pacientes previamente expuestos en comparación con uno sólo entre los 13 pacientes que reaccionaron después de la primera exposición a la altesina.

*Br. J. Anaesth.* (1982), 54, 865

# ANAESTHESIA FOR OUTPATIENT TERMINATION OF PREGNANCY

## *A comparison of two anaesthetic techniques*

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### SUMMARY

Inhalation anaesthesia with enflurane was compared with i.v. fentanyl for outpatient termination of pregnancy. Blood loss was greater in the enflurane group with a geometric mean loss of 73.0 ml compared with 43.9 ml in the fentanyl group. There was a greater frequency of nausea and vomiting in the fentanyl group and no reduction in abdominal pain or need for analgesia after operation. A close relationship was found between blood loss and duration of the procedure but not between blood loss and gestational age or gestational age and anaesthetic time. Either technique is satisfactory for outpatient termination of pregnancy in unpremedicated patients. Despite the greater blood losses with enflurane, it is a safe and reliable method of anaesthesia for this procedure, but the concentration and duration of administration should be kept to a minimum.

Approximately 150 000 operations for termination of pregnancy are performed annually in England and Wales. Eighty-five percent of procedures are vacuum aspirations performed under general anaesthesia at less than 14 weeks gestation (Abortion Statistics, 1979). During 1979, this procedure was performed on 22 036 outpatients. Outpatient surgery makes efficient use of both manpower and facilities and many patients prefer it. It is expected that the amount of outpatient surgery will increase.

Although aspiration termination of pregnancy performed before 12 weeks gestation is a safe procedure, uterine haemorrhage remains a potential hazard. Loung, Buckle and Anderson (1971) found that in a series of 1000 patients, 309 lost more than 200 ml of blood. Cullen, Margolis and Eger (1970) found that blood loss was greater during halothane or fluroxene anaesthesia than when using nitrous oxide with adjuvants or paracervical block. Dunn and colleagues (1973) in their study on blood loss in termination of pregnancy compared four anaesthetic techniques: (1) thiopentone, nitrous oxide, oxygen and trichloroethylene; (2) diazepam, pentazocine, incremental doses of methohexitone and paracervical block; (3) thiopentone, suxamethonium and hyperventilation with nitrous oxide and oxygen; (4) ketamine and paracervical block. They found that blood loss (approximately 250 ml) during trichloroethylene anaesthesia was about five times that associated with the other three techniques. Van Damme and Berre (1976) compared blood loss in two groups of patients undergoing therapeutic abortion during the first trimester of pregnancy. Operation in the first group was performed under paracervical block and in the second group under general anaesthesia with thiopentone, nitrous oxide, oxygen and enflurane. General anaesthesia resulted in significantly larger blood losses, but the absolute blood losses were less than 50 ml in both groups. However, many of these studies depended on inaccurate methods to assess blood loss and most were carried out on inpatients whose premedication may have masked side-effects of drugs.

Grant (1980) stated that, despite these studies, there was no clear evidence to suggest any one general anaesthetic technique was more or less likely to induce serious haemorrhage during surgical termination of pregnancy.

This study was undertaken to assess the blood loss and anaesthetic morbidity in unpremedicated day patients undergoing suction termination of pregnancy of less than 12 weeks gestation using either an inhalation or an i.v. technique.

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## PATIENTS AND METHODS

### *Clinical procedure*

Eighty-two consecutive patients undergoing outpatient termination of pregnancy were studied and allocated randomly to one of two groups. All patients were in A.S.A. assessment Class I or II. No premedication was given. In the enflurane group (E) anaesthesia was induced with methohexitone 2 mg $kg^{-1}$ and maintained with 70% nitrous oxide, 30% oxygen and 3% enflurane until cervical dilatation was completed, when the enflurane was discontinued. The fentanyl group (F) received fentanyl 1.5 μg $kg^{-1}$ i.v. followed by methohexitone 2 mg $kg^{-1}$ and maintained with 70% nitrous oxide and 30% oxygen and incremental doses of methohexitone. In all patients, oxytocin 5 u. was administered at the onset of cervical dilatation.

Blood loss was measured according to the method described by Garrioch, Gilbert and Plantevin (1981). A polythene bag was attached around the introitus on completion of the perineal draping so that all uterine loss, other than that removed by aspiration, was collected. Karmen curettes and aspiration tubing were washed free of products. The products of termination and blood stained swabs were made up to 750 ml and mixed with an equal volume of 10% sodium hydroxide. The alkaline haematin method of Hallberg and Nilsson (1964) was used to determine blood volume. Experiments showed results to vary less than 3% and the stored solution had a half-life of 12 weeks stored at room temperature and in darkness. In practice, measurements were made within 20–72 h of operation.

Duration of operation and the frequency of minor complications such as coughing, salivation, hiccup, laryngeal stridor and limb movements during anaesthesia were noted.

In the recovery room, observations were made by the nursing staff who did not have access to the trial code. Recovery of consciousness was assessed as the time at which the patient first opened her eyes in response to her name. The frequency of nausea and vomiting, abdominal pain and the need for medication after operation were noted by the recovery room staff during the 1st hour and each subsequent hour after operation until discharge.

### *Statistical analysis*

A group sequential design was used to determine the trial size (see Appendix). Monitoring was based on nausea and vomiting since insufficient information on blood loss was available before the trial. The anaesthetic agent was considered a "failure" for a particular patient if she had either moderate or severe nausea with or without vomiting at any time between awakening and discharge. The upper boundary was crossed after 74 patients had been assessed, indicating a statistically significant difference between the two groups at the 5% level using a one-sided test. Owing to the time lag between entry into the trial and assessment, a further eight patients were included, giving a total of 82 patients, 43 in the enflurane group and 39 in the fentanyl group.

The Chi-square test and Student's *t* test were used to evaluate differences between the two groups. Values were considered significant if $P < 0.05$. Logarithms of blood loss were taken to reduce skewness and regression analyses were performed to relate blood losses to anaesthetic agent, gestational age, weight and anaesthetic time.

## RESULTS

There were no statistically significant differences between the groups with respect to age (range 15–45 yr in the enflurane group and 16–39 yr in the fentanyl group, mean 24 yr in both groups), weight (mean 60.5 ± 1.65 kg in the enflurane group and 58.8 ± 1.43 kg in the fentanyl group), medical condition or previous anaesthetic complications. Fifty-nine percent of patients had received a previous general anaesthetic.

Table I shows the results for gestational age, anaesthetic time, recovery time and anaesthetic complications. Complications were classified as minor if they did not interfere with anaesthesia or surgery and as severe if the procedure was delayed.

### *Anaesthetic morbidity*

The duration of operation and recovery time was similar in both groups of patients. Minor anaesthetic complications, mainly hiccup, occurred in 21 of 43 (49%) patients in the enflurane group and 17 of 39 (44%) patients in the fentanyl group. Severe complications occurred in four patients: one patient in the fentanyl group had respiratory depression; prolonged coughing with salivation occurred in one patient in the enflurane group and two patients in the fentanyl group.

### *Blood loss*

Blood losses are shown for each patient in figure 1, with the geometic mean loss and the 95%

TABLE I. *Gestational age, duration of anaesthesia, recovery time and anaesthetic complications in two groups of patients. n.s. = not significant* (P > *0.05*). **1 case excluded because of recording error*

| | Enflurane ($n = 43$) | Fentanyl ($n = 39$) | $\chi^2$ | $P$ |
|---|---|---|---|---|
| Gestation (weeks) | | | | |
| 5–6 | 1 | 1 | | |
| 7–8 | 9 | 7 | 2.61 | n.s. |
| 9–10 | 22 | 26 | | |
| 11+ | 11 | 5 | | |
| Mean | 9.7 | 9.3 | | |
| Anaesthetic time (min) | | | | |
| Range | 7–15 | 6–20* | | |
| Mean | 10.6 | 10.8 | | n.s. |
| SEM | (0.38) | (0.51) | | |
| Recovery time (min) | | | | |
| Range | 1–20 | 1–18 | | |
| Mean | 7.0 | 6.8 | | |
| SEM | (0.55) | (0.66) | | |
| Anaesthetic complications | | | | |
| Nil | 21 (49%) | 19 (48%) | | |
| Minor | 21 (49%) | 17 (44%) | 1.32 | n.s. |
| Severe | 1 (2%) | 3 (8%) | | |

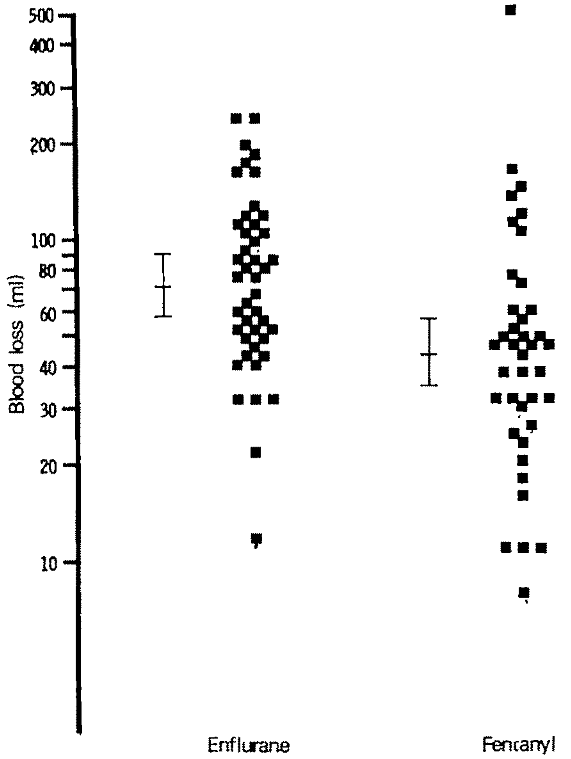

FIG. 1. Blood losses for each patient at vaginal termination of pregnancy, the geometric mean loss and 95% confidence limits in the two treatment groups.

confidence limits. Although the greatest individual loss (480 ml) occurred in the fentanyl group, the geometric mean losses were 73 ml for enflurane and 43.9 ml for fentanyl; the difference being statistically significant ($F_{1.75} = 14.1$, $P < 0.001$). Figure 2 shows the positive relationship between blood loss on the log scale and anaesthetic time (after allowing for treatments; $F_{1.75} = 18.3$, $P < 0.001$). There was no significant relationship between log blood loss and gestational age or between anaesthetic time and gestational age.

*Nausea and vomiting*

Ten patients in the fentanyl group complained of moderate to severe nausea and vomiting compared with only three in the enflurane group. The adjusted percentage allowing for the design of the trial showed a frequency of 24% in the fentanyl group and 8% in the enflurane group which was a significant difference ($P < = 0.024$). A further six patients in the fentanyl group and three in the enflurane group complained of slight nausea.

*Abdominal pain*

Abdominal pain was recorded as slight, moderate or severe. The figures are shown in table II. Frequency of pain was the same in both groups and there was no difference in the analgesic requirements after operation.

TABLE II. *Frequency of abdominal pain and analgesic requirement in two groups of patients. n.s. = not significant,* P > *0.05*

| | Enflurane ($n = 43$) (%) | Fentanyl ($n = 39$) (%) | $P$ |
|---|---|---|---|
| Abdominal pain | | | |
| Nil | 14 (33) | 14 (36) | n.s. |
| Slight | 20 (47) | 15 (39) | n.s. |
| Moderate/severe | 13 (30) | 10 (26) | n.s. |
| Analgesics given | 18 (42) | 16 (41) | n.s. |

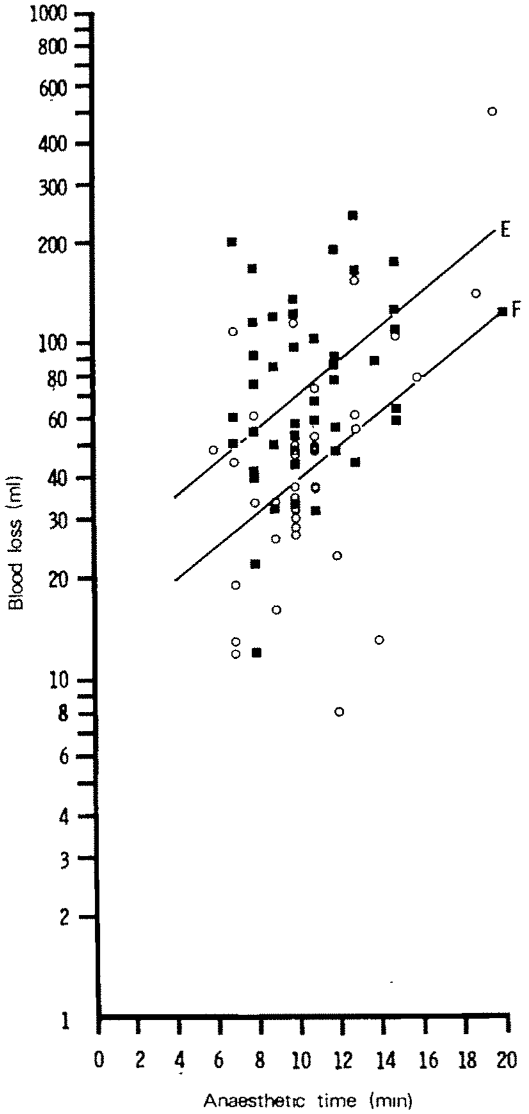

FIG. 2. The relationship between blood loss and anaesthetic time in two groups of patients. ■ = enflurane; ○ = fentanyl.

## DISCUSSION

This is the first report of the use of enflurane for outpatient termination of pregnancy in unpremedicated patients.

Enflurane is particularly suitable for outpatient surgery because of its ease of administration, rapid recovery and relatively low frequency of side-effects. However, *in vitro* studies have shown it to cause myometrial depression (Paull and Ziccone, 1980) which could lead to increased blood loss, although relatively few studies have been carried out *in vivo*. The depressant effect on the myometrium appears to be related both to the concentration of the inhalation agent (Marx et al., 1978) and to the duration of the procedure. Fentanyl was used as it has no known effect on the pregnant uterus and is therefore unlikely to contribute to bleeding during termination of pregnancy. In this study, a greater blood loss did occur in the enflurane group, but the geometric mean loss did not exceed 73.0 ml, compared with 43.9 ml in the fentanyl group.

Previous work has shown a relationship between gestational age and blood loss (Report, 1974) but no relationship was found in this study. The design of the trial allowed a statistically significant difference between the two groups on nausea and vomiting to be detected when only 74 patients had been assessed. A fixed-sample trial would have required 130 patients. However, against the advantage of achieving significance at an early stage is the fact that the small number of patients did not permit detection of possibly significant relationships between blood loss and gestational age and between gestational age and anaesthetic time.

There was a significant relationship between blood loss and duration of the procedure. Blood loss during termination of pregnancy performed under local anaesthesia has been shown consistently to be less than when it is performed under general anaesthesia. This could be caused by the stress response being obtunded by local anaesthesia, but agents used during general anaesthesia may also be responsible for the increased bleeding. In this series, although the blood loss was significantly greater in the enflurane group, the increase in blood loss with anaesthetic time was the same in both groups and some other common factor, such as nitrous oxide, could be implicated as having a depressant effect on the myometrium.

Nausea and vomiting is a common problem with termination of pregnancy and may be associated with the emotional state of the patient, the ecbolic agent used and the anaesthetic technique. This study confirms the low frequency of nausea and vomiting with enflurane and oxytocin.

Hunt, Plantevin and Gilbert (1979) found that fentanyl significantly reduced the frequency and the severity of abdominal pain on the day of operation. In this series, abdominal pain was not improved by the use of fentanyl in the anaesthetic technique and the analgesic requirements of the two groups were the same. This difference may be caused by our observations being continued only until the patient left the recovery room, some 2–3 h after operation and based on nursing staff assessment and not on a patient questionnaire.

The anaesthetic technique used did not affect the time from induction of anaesthesia to entry into the operating theatre and we found no difference in recovery of consciousness between the two groups.

We suggest that either technique is satisfactory for this procedure and that, despite the greater blood losses with enflurane, it is a safe and reliable method of anaesthesia for outpatient termination of pregnancy in unpremedicated patients.

## APPENDIX

### THE GROUP SEQUENTIAL DESIGN— COMPARISON WITH FIXED SAMPLE DESIGN

To determine the sample size for a fixed sample trial and compare a standard and a new treatment, it is necessary to make estimates of, or choose values for, the following four parameters:

(i) the "success" rate of the standard treatment;

(ii) the size of improvement in success rate between the new and standard treatment that the trial hopes to detect;

(iii) the significance level to be used in testing for a difference in success rates between the two treatments (conventionally 5%);

(iv) the power—this is the probability of finding a statistically significant difference if the true difference between the treatments is as large as we hope.

From these four values we can calculate appropriate sample sizes.

The design of a group sequential trial again requires values for the same four parameters and the intended frequency of examination of the data (Whitehead, 1982; Whitehead and Stratton, 1982). Each time the data are examined, a measure of the difference between the treatments is plotted against a measure of the amount of information available. The trial is terminated when the graph crosses predetermined boundaries, the position of which are calculated using the five parameter values.

In the trial described above we decided to use as our measure of difference in success rates:

$$Z = \frac{\dfrac{\text{no. of successes on E}}{\text{no. on E}} - \dfrac{\text{no. of successes on F}}{\text{no. on F}}}{(\text{total no. in trial})/(\text{no. on E} \times \text{no. on F})}$$

The corresponding measure of the amount of information was: $V = (\text{no. on E}) \times (\text{no. on F}) \times (\text{total no. of successes}) \times (\text{total no. of failures})/(\text{total no. in trial})^3$

Our five parameter values were:

(i) estimated rate on F = 80%;

(ii) anticipated success rate on E = 95% (so difference = 15%);

(iii) significance level = 5%;

(iv) power = 90%;

(v) data to be examined at monthly intervals (about every 20 patients).

This choice of parameters leads to the boundaries being fixed at $Z = 2.198 + 0.438$ and $Z = -2.198 + 1.314$. The upper boundary is crossed if E has a higher success rate than F, the lower boundary if E is no better or worse than F.

The data were examined four times: after results were available for 15, 19, 62 and 74 patients. At the last examination of the data, the graph crossed the upper boundary (fig. 3).

An equivalent fixed sample trial would have needed 65 patients on each treatment.

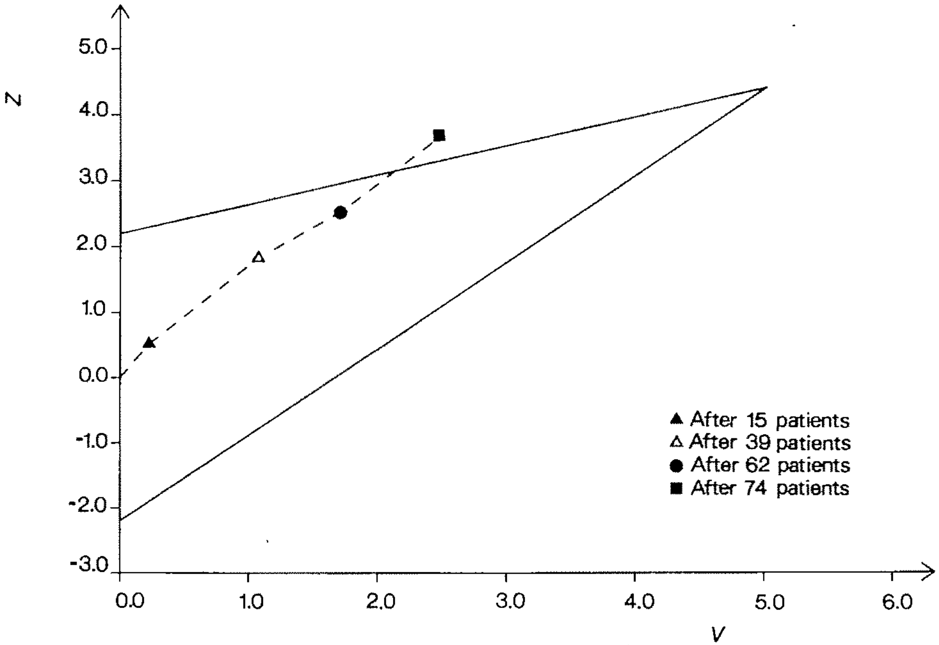

FIG. 3. Plot used in monitoring the trial.

### ACKNOWLEDGEMENTS

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### REFERENCES

Abortion Statistics (1979), England and Wales. Office of Population Censuses and Surveys. Series AB No. 6. London: HMSO.

Cullen, B. F., Margolis, A. J., and Eger, E. I. (1970). The effects of anesthesia and pulmonary ventilation on blood loss during elective therapeutic abortion. *Anesthesiology*, **32**, 108.

Dunn, S. R., Walker, J. S., Aston, D. L., and Cripps, D. (1973). Effect of anaesthetic technique on blood loss in termination of pregnancy. *Br. J. Anaesth.*, **45**, 633.

Garrioch, D. B., Gilbert, J. R., and Plantevin, O. M. (1981). Choice of ecbolic and the morbidity of daycase termination of pregnancy. *Br. J. Obstet. Gynaecol.*, **88**, 1029.

Grant, I. S. (1980). Anaesthesia for termination of pregnancy. *Br. J. Anaesth.*, **52**, 711.

Hallberg, L., and Nilsson, L. (1964). Determination of menstrual blood loss. *Scand. J. Clin. Lab. Invest.*, **16**, 244.

Hunt, T. M., Plantevin, O. M., and Gilbert, J. R. (1979). Morbidity in gynaecological daycase surgery. A comparison of two anaesthetic techniques. *Br. J. Anaesth.*, **51**, 785.

Loung, K. C., Buckle, A. E. R., and Anderson, M. M. (1971). Results in 1,000 cases of therapeutic abortion managed by vacuum aspiration. *Br. Med. J.*, **4**, 477.

Marx, G. F., Kim, K. I., Lin, C., Harvey, S., and Schulman, H. (1978). Postpartum uterine pressures under halothane or enflurane anaesthesia. *Obstet. Gynaecol.*, **51**, 695.

Paull, J., and Ziccone, S. (1980). Halothane, enflurane, methoxyflurane and isolated human uterine muscle. *Anaesth. Intens. Care*, **8**, 397.

Report (1974). Report of the Committee on the Working of the Abortion Act (1974). Volume I, p. 47. Chair: Hon. Mrs Justice Lane. London: HMSO.

Van Damme, C., and Berre, J. (1976). Influence of enflurane on blood loss from the pregnant uterus. *Acta Anesthesiol. Belg.*, **27**, (Suppl.), 259.

Whitehead, J. (1982). *The Design and Analysis of Sequential Clinical Trials.* Chichester: Ellis Horwood (in press).

—— Stratton, I. (1982). *Group Sequential Clinical Trials with Triangular Continuation Regions.* (In press).

## ANESTHESIE POUR INTERRUPTION DE GROSSESSE EN AMBULATOIRE

*Une comparaison de deux techniques anesthesiques*

### RESUME

Une anesthésie par inhalation à l'enflurane a été comparée au fentanyl intra-veineux pour l'interruption de grossesse ambulatoire. Le saignement était plus important dans le groupe enflurane avec une moyenne géométrique des pertes de 73,0 ml, comparée à 43,9 ml dans le groupe fentanyl. Les nausées et les vomissements étaient plus fréquents dans le groupe fentanyl sans que la douleur abdominale ou le besoin d'analgésie post-opératoir soient moindres. Il est apparu une relation étroite entre le saignement et la durée de l'acte mais pas entre le saignement et l'âge gestationnel ni entre l'âge gestationnel et la durée de l'anesthésie. Les deux techniques sont satisfaisantes pour l'interruption ambulatoire de grossesse chez des patientes non prémédiquées. Malgré les pertes sanguines plus importantes avec l'enflurane, c'est une méthode sure et fiable d'anesthésie pour cet acte, mais la concentration et la durée d'adminstration de l'enflurane doivent être limitées le plus possible.

## ANÄSTHESIE FÜR AMBULANTE ABRUPTIO

*Vergleich von zwei Narkosearten*

### ZUSAMMENFASSUNG

Die Inhalationsnarkose mit Enflurane wurde mit i.v. Fentanyl für die ambulante Abruptio verglichen. Der Blutverlust war größer in der Enflurane-Gruppe mit einem durchschnittlichen Blutverlust von 73 ml im Vergleich zu 43,9 ml in der Fentanyl-Gruppe. Übelkeit und Erbrechen traten in der Fentanyl-Gruppe häufiger auf, aber postoperativ waren keine Analgetikagaben notwendig. Es stellte sich eine enge Beziehung zwischen Blutverlust und Dauer des Eingriffs heraus, aber nicht zwischen Blutverlust und Schwangerschaftsmonat und Narkosedauer. Jede Technik ist zufriedenstellend für ambulante Abruptio bei unprämedizierten Patienten. Trotz des höheren Blutverlustes bei der Enflurane-Narkose ist sie eine sichere und verläßliche Methode für diesen Eingriff, aber die Konzentration und die Dauer Anwendung sollten so niedrig wie möglich gehalten werden.

## ANESTESIA PARA TERMINACION DE EMBARAZO EN PACIENTES NO RESIDENTES: COMPARACIÓN DE DOS TÉCNICAS ANESTÉSICAS

### SUMARIO

La inhalación de anestesia con enflurano se comparó con la administración intravenosa de fentanilo en la terminación de embarazo en pacientes no residentes. La pérdida de sangre fue superior en el grupo de enflurano, presentando una pérdida con media geométrica de 73,0 ml en comparación con 43,9 ml para el grupo de fentanilo. El grupo sometido a fentanilo presentó una mayor frecuencia de náuseas y vómitos sin reducción alguna del dolor abdominal y sin necesidad de analgesia postoperativa. Se apreció una estrecha relación entre la pérdida de sangre y la duración del proceso, no siendo éste el caso entre la pérdida de sangre y la edad de gestación ni entre la edad de gestación y el tiempo de duración de la anestesia. Ambas técnicas son satisfactorias para la terminación de embarazos en pacientes no residentes sin premedicación. A pesar de la mayor pérdida de sangre en el caso del enflurano, éste es un método seguro y de confianza para la anestesia tendente a dicho fin, aunque la concentración y la duración de la administración debe mantenerse al mínimo.

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# COMPARATIVE PHARMACOKINETICS OF FENTANYL AND ALFENTANIL

S. BOWER AND C. J. HULL

## SUMMARY

The pharmacokinetics of fentanyl and alfentanil were compared by the simultaneous i.v. administration of both drugs, measurement of plasma concentrations and compartmental analysis. In addition, plasma protein binding, erythrocyte:plasma partition, and heptane:water partition were compared. Alfentanil was found to have a very much smaller apparent volume of distribution, smaller total clearance, and shorter terminal half-time in plasma. Alfentanil was also found to have a greater plasma protein binding, but in contrast to fentanyl, no binding to erythrocytes. It is concluded that alfentanil is less cumulative than fentanyl, has restricted hepatic clearance, and will exhibit non-linear kinetics at very high doses. An appendix describes the model-fitting procedure in detail.

The new synthetic opioid alfentanil has been shown to have a very short duration of action in small animals (Niemegeers, 1977; Brown, Pleuvry and Kay, 1980). Whilst of longer duration in man, alfentanil appears to be very short-acting in comparison with other opioids such as fentanyl, and to be less cumulative (Kay and Pleuvry, 1980; Kay and Stephenson, 1980). As a component of total i.v. anaesthesia and for the supplementation of inhalation anaesthesia, these characteristics are highly desirable.

It is important to compare the disposition of alfentanil with that of fentanyl in order to establish a firm pharmacokinetic basis for clinical technique. This study compares the general pharmacokinetics* of the two agents in healthy volunteers and relates the results to plasma protein and erythrocyte binding data from the same subjects. By simultaneous administration of both drugs, the method seeks to overcome the problem of variation within subjects in a necessarily small series, and by the use of an infusion technique, that of delayed mixing in plasma following bolus doses. The lipid solubilities of both agents were compared by estimation of the heptane:water partition coefficients, and the binding to plasma proteins was measured by equilibrium dialysis.

## METHODS

### (1) *General pharmacokinetics*

The study was performed in five male and two female healthy volunteers aged 24–60 yr and weighing 55–84 kg (table I). Concentrations of total serum protein, serum albumin, haemoglobin and erythrocytes were within normal limits in each case. The method was approved by the University of Newcastle upon Tyne Ethics Committee.

In each experiment, the subject was given a light, non-fatty breakfast and, at least 1 h later, confined to bed for the duration of the trial. After a 30-min rest period, an infusion needle was placed in a vein on the dorsum of the right hand, and a 16-gauge cannula inserted to a forearm vein of the left arm. A solution containing fentanyl and alfentanil was infused at a constant rate through the needle, such that approximately 170 μg of each drug was given over a period of 2.5 min (table I). The precise dose of each drug was determined by weighing.

TABLE I. *Subject data and doses of fentanyl and alfentanil given in the simultaneous infusion study*

| Subject | Sex | Age (yr) | Wt. (kg) | Fentanyl dose (μg) | Alfentanil dose (μg) |
|---|---|---|---|---|---|
| 1 | F | 35 | 54.9 | 164.41 | 161.74 |
| 2 | M | 42 | 82.0 | 170.05 | 170.24 |
| 3 | F | 46 | 61.2 | 167.03 | 163.70 |
| 4 | M | 35 | 76.0 | 164.40 | 163.19 |
| 5 | M | 60 | 65.1 | 164.16 | 167.46 |
| 6 | M | 24 | 69.2 | 164.32 | 159.86 |
| 7 | M | 37 | 83.8 | 163.70 | 163.03 |

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*Symbols used in this paper are listed in Appendix B. See also Hull (1979a, b).

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Venous blood samples were taken at 2-min intervals from 0 to 12 min, and then at increasing intervals until half-hourly sampling was adopted between 90 and 360 min. The experiment was terminated at 360 min. During the sampling period the subject was allowed only water by mouth.

To compare the observed pharmacokinetic characteristics of alfentanil with those at larger (clinical) doses, the experiment was repeated in five of the subjects at least 3 weeks later when alfentanil 1 mg alone was given by i.v. infusion over 2.5 min.

*Assay of fentanyl and alfentanil in plasma.* Separated plasma from the venous blood samples was stored at −20 °C until assay. A radioimmunoassay technique of sensitivity 2 pg/ml plasma was used to measure plasma concentrations of fentanyl (Bower, 1980). This assay was based on a less sensitive method described by Michiels, Hendriks and Heykants (1977). A radioimmunoassay of sensitivity similar to that for fentanyl was devised to measure plasma concentrations of alfentanil. [$^3$H]-alfentanil and rabbit anti-alfentanil antibody were obtained from Janssen Pharmaceutica, Beerse, Belgium, and [$^3$H]-fentanyl was obtained from I.R.E. Brussels. All samples were assayed in triplicate.

The cross-reaction of each drug in assay for the other was negligible, the recognition of each drug by the opposite antibody being less than $10^{-4}$ that of the appropriate drug, on a molar basis.

*Derivation of a pharmacokinetic model from the post-infusion data.* A two-compartment open model was fitted to each set of data using a lattice-search technique, which minimized the differences between the measured concentrations and those derived from the model. A detailed account is to be found in Appendix A.

Values of apparent volume of distribution ($V^{ss} = V_1 + V_2$), terminal half life ($T_{\frac{1}{2}}^{\beta} = \ln 2/\beta$), and total clearance ($Cl = V_1 . k_{10}$) were calculated from the model parameters (see Hull, 1979a, b). Student's $t$ test (paired data) and the correlation coefficient ($r$) were used to compare the results of the low-dose study. The high-dose data for alfentanil were compared with those at the lower dose using unpaired $t$ tests. Where the $F$ ratio was significant, Cochrane's modification of the $t$ test was used.

### (2) *Binding studies with plasma proteins and erythrocytes*

The binding of fentanyl to normal plasma proteins was previously measured by equilibrium dialysis in 15 healthy volunteers, including six of the present subjects (Bower, 1981). The binding of alfentanil was determined in 14 of these subjects by the same technique.

The partition coefficient ($\lambda_{RP}$) of fentanyl between normal red cells and plasma has been measured by recovery of tritiated drug from separated plasma after equilibration in whole blood and by equilibrium dialysis (Bower, 1982). The percent of drug within red cells which is bound to the erythrocyte ($Br\%$) was measured by equilibrium dialysis of washed red cells against phosphate buffer 0.1 mol litre$^{-1}$ (pH 7.4). These methods were applied to determine the partition of alfentanil between red cells and plasma.

### (3) *Heptane: water partition coefficients*

The heptane: water partition coefficient ($\lambda_{HW}$) of each drug was measured at 37 °C, pH 7.4, by recovery of tritiated drug from the heptane and aqueous phases after thorough mixing. Sodium phosphate buffer 0.1 mol litre$^{-1}$ (pH 7.4) was used as the aqueous phase.

## RESULTS

Biexponential curves fitted the declining plasma concentrations of both drugs with a percentage fit of > 97% in all cases. Figure 1 illustrates the curve fit for subject 1, and figure 2 superimposes the best-fitting curves for both drugs in all subjects. The disposition of the two drugs was clearly different, and alfentanil concentrations were greater than those for fentanyl at all times. Pharmacokinetic analysis showed that fentanyl had a significantly

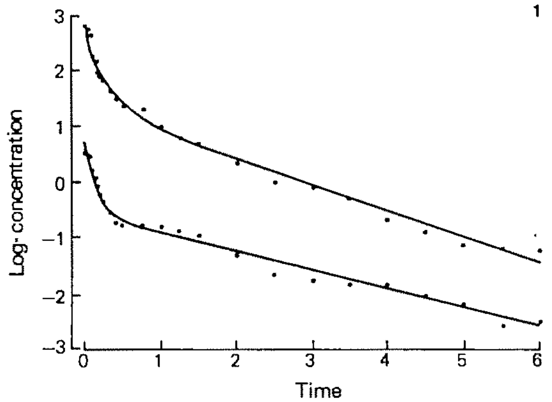

FIG. 1. The log-concentration (in ng ml$^{-1}$)–time (h) data for subject 1, and the log-concentration–time characteristics of best-fitting two-compartment open models for both drugs, after simultaneous i.v. administration. Upper trace: alfentanil; lower trace: fentanyl.

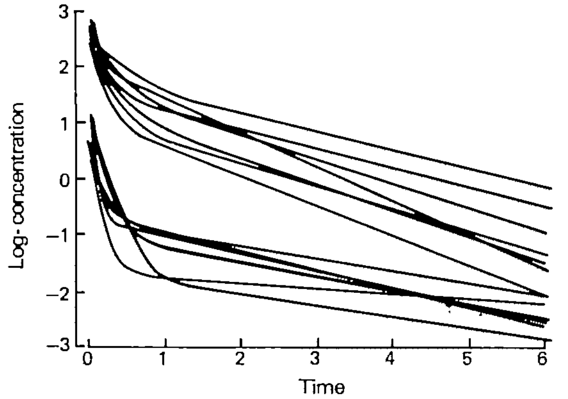

FIG. 2. Log-concentration (in ng ml$^{-1}$)–time (h) data for the two-compartment open models fitted to the data of all subjects given simultaneous doses of fentanyl and alfentanil. Upper group: alfentanil; lower group: fentanyl.

larger distribution volume ($P < 0.05$), elimination half-life ($T_{\frac{1}{2}}^{\beta}$) ($P < 0.05$) and total clearance ($P < 0.001$) than alfentanil (table II, fig. 3).

There was no significant ($P > 0.05$) correlation between age or body weight and any pharmacokinetic variable for either drug (tables I, II); neither did any variable for fentanyl correlate with that for alfentanil, with the exception of $k_{10}$ ($r = 0.804$, $P = < 0.05$). However the result was not significant where values of $k_{10}$ obtained after a dose of alfentanil 1 mg were compared with those for fentanyl. The pharmacokinetic variables for alfentanil 1 mg did not differ significantly from those derived from doses of approximately 170 µg given to the same individuals (table III).

Plasma protein binding of alfentanil was significantly greater ($P < 0.001$) than for fentanyl (table IV). Alfentanil did not bind to red cells and therefore the value of the red cell: plasma partition coefficient was low (table V). Fentanyl binding to red cells was similar in extent to binding to plasma proteins to give uniform distribution of drug between the two phases ($\lambda_{RP}$ = unity) (table V).

Alfentanil is less lipid soluble than fentanyl. At 37 °C, pH 7.4, the heptane: water partition coefficient was 2.5 for alfentanil and 9.0 for fentanyl.

TABLE II. *Pharmacokinetic variables calculated for seven subjects given simultaneous infusions of fentanyl and alfentanil. Each value of* P *indicates the result of a paired* t *test between the results for both drugs. The symbol* † *indicates the use of Cochrane's modification of the unpaired Student's* t *test.* $V_1$, $V_2$ *etc., are the parameters of two-compartment models fitted to the data (see fig. 2).* $T_{\frac{1}{2}}^{\beta}$ *is the half-time for the terminal phase of the corresponding biexponential decay, and* Cl *denotes clearance*

| Subject | % Fit | $V_1$ (litre) | $V_2$ (litre) | $V^{ss}$ (litre) | $k_{12}$ ($h^{-1}$) | $k_{21}$ ($h^{-1}$) | $k_{10}$ ($h^{-1}$) | *Cl* (litre $h^{-1}$) | $T_{\frac{1}{2}}^{\beta}$ (h) |
|---|---|---|---|---|---|---|---|---|---|
| Fentanyl | | | | | | | | | |
| 1 | 99.81 | 67.64 | 168.16 | 235.80 | 5.11 | 2.06 | 1.31 | 88.25 | 2.10 |
| 2 | 99.52 | 34.03 | 223.03 | 257.06 | 11.61 | 1.77 | 2.72 | 92.49 | 2.27 |
| 3 | 99.91 | 57.18 | 249.22 | 306.40 | 3.67 | 0.84 | 1.64 | 93.67 | 2.97 |
| 4 | 99.87 | 54.70 | 286.55 | 341.25 | 3.34 | 0.64 | 2.22 | 121.32 | 2.92 |
| 5 | 99.29 | 91.10 | 196.22 | 287.32 | 3.96 | 1.84 | 0.79 | 72.25 | 3.02 |
| 6 | 99.92 | 47.90 | 221.80 | 269.70 | 4.73 | 1.02 | 1.81 | 86.67 | 2.74 |
| 7 | 97.71 | 65.36 | 584.91 | 650.27 | 10.99 | 1.23 | 1.35 | 88.29 | 5.62 |
| Mean | | 59.70 | 275.70 | 335.40 | 6.20 | 1.34 | 1.69 | 91.85 | 3.09 |
| SD | | 17.85 | 141.42 | 143.00 | 3.54 | 0.55 | 0.64 | 14.77 | 1.17 |
| Alfentanil | | | | | | | | | |
| 1 | 99.96 | 8.94 | 16.22 | 25.16 | 3.24 | 1.79 | 1.71 | 15.26 | 1.42 |
| 2 | 99.98 | 11.10 | 24.18 | 35.28 | 5.39 | 2.47 | 2.11 | 23.38 | 1.25 |
| 3 | 99.97 | 11.00 | 12.25 | 23.25 | 2.21 | 1.98 | 1.11 | 12.29 | 1.52 |
| 4 | 99.87 | 8.26 | 18.26 | 26.52 | 5.12 | 2.31 | 1.27 | 10.49 | 1.97 |
| 5 | 99.68 | 13.04 | 10.17 | 23.21 | 0.91 | 1.17 | 0.61 | 7.91 | 2.34 |
| 6 | 99.98 | 9.15 | 9.34 | 18.49 | 3.76 | 3.68 | 1.36 | 12.41 | 1.14 |
| 7 | 99.91 | 15.17 | 23.52 | 38.69 | 2.47 | 1.59 | 1.20 | 18.24 | 1.76 |
| Mean | | 10.95 | 16.28 | 27.23 | 3.30 | 2.14 | 1.34 | 14.28 | 1.63 |
| SD | | 2.47 | 6.06 | 7.18 | 1.61 | 0.81 | 0.47 | 5.19 | 0.42 |
| *P* | | <0.001† | <0.01† | <0.01† | 0.06 | 0.12 | 0.08 | <0.001† | 0.02† |

TABLE III. *Pharmacokinetic variables calculated for five subjects given alfentanil 1 mg*

| Subject | % Fit | $V_1$ (litre) | $V_2$ (litre) | $V^{ss}$ (litre) | $k_{12}$ (h$^{-1}$) | $k_{21}$ (h$^{-1}$) | $k_{10}$ (h$^{-1}$) | $Cl$ (litre h$^{-1}$) | $T_{\frac{1}{2}}^{\beta}$ (h) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 99.91 | 16.87 | 39.90 | 56.77 | 2.80 | 1.18 | 2.33 | 39.35 | 1.47 |
| 2 | 99.96 | 10.04 | 16.71 | 26.75 | 5.69 | 3.42 | 1.36 | 13.65 | 1.49 |
| 3 | 99.91 | 8.67 | 18.56 | 27.23 | 8.09 | 3.78 | 1.54 | 13.32 | 1.55 |
| 4 | 99.98 | 13.81 | 13.52 | 27.33 | 1.56 | 1.59 | 1.25 | 17.23 | 1.36 |
| 7 | 99.95 | 12.26 | 27.05 | 39.31 | 1.75 | 0.79 | 1.61 | 19.75 | 2.07 |
| Mean | | 12.33 | 23.15 | 35.48 | 3.98 | 2.15 | 1.62 | 20.66 | 1.59 |
| SD | | 3.22 | 10.62 | 13.03 | 2.83 | 1.36 | 0.42 | 10.78 | 0.28 |

## DISCUSSION

The simultaneous administration of equal doses of fentanyl and alfentanil permitted comparison of paired kinetic data under identical conditions. High assay specificity allowed accurate measurement of the concentration of each drug in the presence of the other.

The use of a 2.5-min infusion eliminated early oscillation in drug concentration as a result of non-uniform mixing within the plasma. Identification of the pharmacokinetic model was therefore improved by this technique and also by use of a model-fitting method which reduced the error associated with derivation of kinetic values from the constants of a polyexponential equation (Saunders and Natunen, 1972).

Comparison of the results obtained after an infusion of alfentanil 170 μg or 1 mg showed no significant difference in kinetic constants (tables II, III). The results of the simultaneous infusion study are therefore equally applicable at a clinical dose of alfentanil.

The large differences in time–concentration characteristics for equal doses of the two drugs (fig. 2) cannot be attributed to experimental technique or error, but reflect real differences in the distribution of two related opioids.

The larger distribution volume $V^{ss}$ of fentanyl (table II) is compatible with its greater lipid solubility and also may reflect a higher degree of binding to tissue proteins.

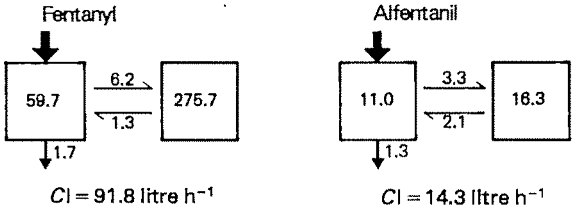

FIG. 3. Mean values for the pharmacokinetic analysis (table II) presented as compartmental diagrams. Rate constants = h$^{-1}$, volumes = litre.

TABLE IV. *Binding (B% ± SEM) of fentanyl and alfentanil to plasma proteins over the concentration range 0.4 ng ml$^{-1}$ to 5 mg ml$^{-1}$. Number of estimations performed at each concentration in parentheses. Fentanyl data taken from Bower (1981)*

| Concentration | Fentanyl | Alfentanil |
|---|---|---|
| 0.4 ng ml$^{-1}$ | 79.16 ± 0.16 (45) | 88.65 ± 0.45 (42) |
| 50.0 ng ml$^{-1}$ | — | 88.53 ± 0.28 (3) |
| 100.0 ng ml$^{-1}$ | 78.29 ± 0.75 (3) | 89.24 ± 0.63 (6) |
| 1.0 μg ml$^{-1}$ | — | 84.27 ± 0.51 (3) |
| 10.0 μg ml$^{-1}$ | 80.53 ± 0.64 (3) | 67.02 ± 0.45 (5) |
| 100.0 μg ml$^{-1}$ | — | 35.16 ± 0.42 (6) |
| 5.0 mg ml$^{-1}$ | 79.73 ± 0.44 (3) | — |

There was no significant difference between the rate constants $k_{12}$, $k_{21}$ and $k_{10}$ for the two drugs (table II). However, total clearance of fentanyl ($Cl = V_1 . k_{10}$) greatly exceeds that of alfentanil, as a function of the larger initial volume of distribution. Renal elimination of fentanyl has been shown to be very low in man (Hess, Stiebler and Herz, 1972; Schleimer et al., 1978), and the major site of elimination is assumed to be the liver. Clearance of fentanyl (91.87 litre h$^{-1}$) approximates to hepatic blood flow (average 90 litre h$^{-1}$ in adult males), which suggests that binding of fentanyl to plasma proteins and red cells is non-restrictive, and that the hepatic extraction ratio approaches unity. En-

TABLE V. *Red cell:plasma partition coefficients ($\lambda_{RP}$) and red-cell binding characteristics (Br%) of fentanyl and alfentanil*

| | No. of subjects | $\lambda_{RP}$ | *Br%* |
|---|---|---|---|
| Fentanyl | 15 | 1.01 ± 0.0083 | 77.53 ± 1.14 |
| Alfentanil | 6 | 0.14 ± 0.02 | 1.05 ± 0.49 |
| *P* | | < 0.001 | < 0.001 |

terohepatic recycling of drug secreted into the stomach is therefore unlikely to cause secondary increase of plasma fentanyl concentration in the systemic circulation, as a result of efficient hepatic extraction of drug from portal venous blood.

Unlike fentanyl, alfentanil does not bind to red cells (table V). Therefore, total clearance of alfentanil must be considered in terms of plasma flow, since alfentanil is present in red cells only in very small quantities (equal to the concentration of free drug in plasma). Total clearance of alfentanil (14.28 litre $h^{-1}$) is approximately one-third of liver plasma flow (average 45 litre $h^{-1}$). Hepatic extraction therefore cannot exceed 0.33, even if clearance resulting from renal elimination is very low. Secondary increases in systemic plasma concentration of alfentanil attributable to enterohepatic circulation are therefore theoretically possible.

The apparently restrictive binding of alfentanil to plasma proteins may be, in part, a result of its greater binding compared with fentanyl (table IV), but is more likely to reflect a greater affinity for plasma proteins. Increased binding to plasma proteins will also contribute to the lower distribution volume of alfentanil (table II).

Although clearance of fentanyl is much greater than for alfentanil, the greater distribution volume to be cleared gives an elimination half-life ($T_{\frac{1}{2}}^{\beta}$) which is twice that for alfentanil (table II).

Bovill and others (1981) have reported the pharmacokinetics of alfentanil after bolus i.v. injection of 50 $\mu g\,kg^{-1}$ and 125 $\mu g\,kg^{-1}$. At both doses the value of $V^{ss}$ and clearance greatly exceeded those of the present study. The final value of $T_{\frac{1}{2}}^{\beta}$ is compatible.

The difference in pharmacokinetic constants obtained at very high doses of alfentanil is likely to be the result of the progressive decrease in percent bound to plasma proteins with plasma concentrations greater than 100 ng $ml^{-1}$ (table IV). An increase in the free fraction is compatible with the observed increased volume of distribution and increased clearance, reported by Bovill and colleagues (1981). These differences should have been even more apparent where 125 $\mu g\,kg^{-1}$ was given, compared with the dose of 50 $\mu g\,kg^{-1}$. That this is not seen, may reflect the large variation in results reported by these authors.

Alfentanil appears to be unique among opioids in having a small apparent volume of distribution and low clearance.

The high clearance of fentanyl appears to be, in part, a result of readily reversible binding to plasma proteins and red cells. The bound fractions serve as a reservoir by which the free concentration of drug in plasma is maintained. The total concentration of fentanyl in whole blood is thus effectively made available for clearance. By contrast, alfentanil appears to have a greater affinity for plasma proteins and is not bound to erythrocytes. The free fraction would be less readily maintained by dissociation of bound drug, and would be compatible with the observed low value of clearance. However, since clinical cumulation is related not to clearance but to drug half-life, alfentanil should be less cumulative than fentanyl. The reduced plasma-protein binding of alfentanil at high concentrations would be expected to result in non-linear kinetics and some enhancement of the concentration–effect relationship at very high doses.

Since the pharmacokinetic characteristics of neither drug appears to be correlated with the age or weight of the subject, it would not be helpful to base dosage upon these factors.

## APPENDIX A

### DETERMINATION OF A TWO-COMPARTMENT OPEN MODEL FROM POST-INFUSION TIME–CONCENTRATION DATA

Conventionally, a curve of the form:

$$C = Ai.e^{-\alpha t} + Bi.e^{-\beta t} \tag{1}$$

is fitted to the time–concentration data using non-linear regression (the constants $A$, $B$ are postscripted i to denote the post-infusion condition). The measured concentrations may be weighted before this procedure if the assay variance is known to be concentration-dependent. The constants $Ai$, $Bi$ are transformed into their non-infusion equivalents $A$, $B$ using:

$$A = \frac{Ai.T.\alpha}{1-e^{-\alpha T}} \quad \text{and } B = \frac{Bi.T.\beta}{1-e^{-\beta T}} \tag{2}$$

Then the parameters of the corresponding model may be calculated using the familiar sequence:

$$\begin{aligned} V_1 &= Xd/(A+B) \\ k_{21} &= A.\beta + B.\alpha/(A+B) \\ k_{10} &= \alpha.\beta/k_{21} \\ k_{12} &= \alpha + \beta - k_{21} - k_{10} \\ V_2 &= V_1.k_{12}/k_{21} \end{aligned} \tag{3}$$

This sequential calculation leads to non-uniformity of confidence in the model parameters, which may become extreme in the case of $k_{12}$ (Saunders and Natunen, 1972).

Since the intention is to propose a *model* which best satisfies the data, it is more logical to determine model parameters whose corresponding *equation* (1) fits the data with least error (Pfeffer, 1973). Clearly, in the case of a "perfect fit" the two processes lead to identical solutions, but in all other cases only the latter method will yield equally confident estimates for all parameters.

As shown by Pfeffer (1973), a least-squares solution can be found by optimizing $k_{12}$, $k_{21}$ and $k_{10}$ only, with subsequent calculation of $V_1$. This reduction to three regression variables simplifies the process greatly, whatever method of convergence is used.

Here, following Pfeffer (1973), an initial estimate is reached by a crude "curve-stripping" routine, followed by equations (3). Then, an estimate is made of a possibly "better" combination of $k_{12}$, $k_{21}$ and $k_{10}$ (see below). The corresponding equation (1) is then calculated, and a prediction made for concentration at each of the "observed" times. The sum of the squared, weighted differences between "observed" and "predicted" concentrations (SSQ) is then calculated, compared with the initial value, and the new set of parameters accepted or rejected accordingly. With successive iterations, the solution converges rapidly to an optimum set of parameters at which SSQ is minimized.

The parameters $k_{12}$, $k_{21}$ and $k_{10}$ can be visualized as a three-dimensional space (the so-called parameter space). If SSQ is calculated for all possible combinations of parameters, the solutions form a surface in the fourth dimension (this can be conceived as a range of values in another quantity: say light → dark).

Unless there is a perfect fit to the data, the solution surface will be characterized by multiple minima, so that simple "slope" methods will tend to find one minimum and ignore others (elsewhere in the parameters space) which may be "lighter". Thus the initial estimate may have a profound effect upon the final solution. Pfeffer's method seeks to overcome this difficulty by surveying the parameter space around a given solution (calculated by a gradient method) before it is accepted.

Here, the optimum values of $k_{12}$, $k_{21}$ and $k_{10}$ are found by a direct search method, in which the initial estimate has very little effect upon the result. The parameter space around each estimate is explored by a three-dimensional lattice with a 2% interval (range ± 6% of all three parameters). The estimate is moved to the coordinate with minimum SSQ, and the process repeated for any "new" space within ± 6% of all parameters. When no improving move can be found, the lattice increment is increased to 8% and the process repeated, covering the range ± 24% of all parameters. If a new solution zone is found, the 2% search is repeated, and so on. Finally, a 0.2% search (± 0.6%) is made, to define the solution in detail. This procedure makes no assumptions as to the solution function, and does not "lead" the parameters towards any particular solution zone.

*Calculation of* A, B, *α, β from an estimate of* $k_{12}$, $k_{21}$, $k_{10}$

Since this procedure is fundamental to the method, and is not described elsewhere, it is set out in some detail:

(1) Calculate α, β

Given $P = k_{12} + k_{21} + k_{10}$ and $Q = \sqrt{P^2 - (4 \times k_{21} \times k_{10})}$

$$\alpha = (P+Q)/2 \quad \text{and} \quad \beta = (P-Q)/2 \qquad (4)$$

(2) Calculate $V_1$

Here, Pfeffer's calculation is developed to include post-infusion data. $V_1$ can be calculated from any single time–concentration datum (i.e. one of the original data values).

Given: $C$ = known concentration at time $t$ after infusion ended

$T$ = duration of infusion

$k'_{01}$ = infusion rate

$W = (k_{21} - \alpha)(e^{-\alpha T} - 1)/\alpha$

$X = (\beta - k_{21})(e^{-\beta T} - 1)/\beta$

$Y = k_{01}'/(\alpha - \beta)$

$$V_1 = \frac{Y.W.e^{-\alpha t} + X.e^{-\beta t}}{C} \qquad (5)$$

$V_1$ is calculated thus for all the time–concentration data points, and averaged to reach an optimum solution. This is a powerfully convergent step, since all known data are used to reach the best possible value of $V_1$ for any postulated set of $K_{12}$, $k_{21}$, $k_{10}$.

(3) Calculate infusion constants *A*i and *B*i

$$Ai = Y.W/V_1 \quad \text{and} \quad Bi = Y.X/V_1 \qquad (6)$$

(4) Equation (1) can now be solved for any time $t$ and compared with the known concentration.

Although this method was developed to analyse data after 2.5-min infusions, it can be used with advantage in any single-dose kinetic study where the administration time is finite, since it eliminates the error caused by the usual assumption that $T = 0$.

The analysis program was written in extended BASIC, and run on an HP.85 computer.

## APPENDIX B

### SYMBOLS

| | |
|---|---|
| $C$ | Concentration at any time $t$ (ng ml$^{-1}$) |
| α, β | Rate constants characterizing a bi-exponential decay function (h$^{-1}$) |
| $A$, $B$ | Constants (ng ml$^{-1}$) |
| *A*i, *B*i | Post-infusion equivalents of *A*, *B* |
| $V_1$, $V_2$ | "Central and "deep" compartmental volumes (litre) |
| $V^{ss}$ | Total apparent volume of distribution, defined at an infusion steady state (litre) |
| $k_{12}$ | Rate constant for drug transfer from compartment 1 to compartment 2 (h$^{-1}$) |
| $k_{21}$ | Rate constant for drug transfer from compartment 2 to compartment 1 (h$^{-1}$) |
| $k_{10}$ | Elimination rate constant from compartment 1 (h$^{-1}$) |
| *X*d | Dose (ng) |
| *Cl* | Total clearance (litre h$^{-1}$) |
| $k'_{01}$ | Infusion rate (ng h$^{-1}$) |
| $T$ | Infusion time (h) |
| $t$ | Any specified time following the infusion (h) |
| $T_{\frac{1}{2}}^{\beta}$ | Half-time of the terminal phase of a biexponential decay function (h) |
| $\lambda_{RP}$ | Red-cell: plasma partition coefficient at pH 7.4, 37 °C |
| $\lambda_{HW}$ | Heptane: water partition coefficient at pH 7.4, 37 °C |
| *B*% | Percentage binding to plasma proteins at pH 7.4, 37 °C |
| *B*r% | Percentage binding to red cells at pH 7.4, 37 °C |

### REFERENCES

Bovill, J. G., Sebel, P. S., Blackburn, C. L., and Heykants, J. (1981). The pharmacokinetics of alfentanil. *Anesthesiology*, 55, A174.

Bower, S. (1980). The Measurement and Distribution of Fentanyl in Blood. Ph.D. Thesis, University of Newcastle upon Tyne.

Bower, S. (1981). Plasma protein binding of fentanyl. *J. Pharm. Pharmacol.*, **33**, 507.

—— (1982). The uptake of fentanyl by erythrocytes. *J. Pharm. Pharmacol.*, 34, 181.

Brown, J. H., Pleuvry, B., and Kay, B. (1980). Respiratory effects of a new opiate analgesic R 39209, in the rabbit: comparison with fentanyl. *Br. J. Anaesth.*, 52, 1101.

Hess, R., Stiebler, G., and Herz, A. (1972). Pharmacokinetics of fentanyl in man and rabbit. *Eur. J. Clin. Pharmacol.*, 4, 137.

Hull, C. J. (1979a). Symbols for compartmental models. *Br. J. Anaesth.*, 51, 815.

—— (1979b). Pharmacokinetics and pharmacodynamics. *Br. J. Anaesth.*, 51, 579.

Kay, B., and Pleuvry, B. (1980). Human volunteer studies of alfentanil (R 39209), a new short-acting narcotic analgesic. *Anaesthesia*, 35, 952.

—— Stephenson, D. K. (1980). Alfentanil (R 39209): initial experience with a new narcotic analgesic. *Anaesthesia*, 35, 1197.

Michiels, M., Hendricks, R., and Heykants, J. (1977). A sensitive radioimmunoassay for fentanyl. *Eur. J. Clin. Pharmacol.*, 12, 153.

Niemegeers, C. J. E. (1977). R 39209, a potent and very short-acting morphine-like analgesic. Janssen Pharmaceutica: Preclinical Research Report.

Pfeffer, M. (1973). COMPT, a time-sharing program for nonlinear regression analysis of compartmental models of drug distribution. *J. Pharmacokinet. Biopharm.*, 1, 137.

Saunders, L., and Natunen, T. (1972). A statistical approach to pharmacokinetic calculations. *J. Pharm. Pharmacol.*, 24, (Suppl.) 94P.

Schleimer, R., Benjamini, E., Eisele, J., and Henderson, G. (1978). Pharmacokinetics of fentanyl as determined by radioimmunoassay. *Clin. Pharmacol. Ther.*, 23, 180.

## PHARMACOCINETIQUES COMPAREES DU FENTANYL ET DE L'ALFENTANIL

### RESUME

Les pharmacocinétiques du fentanyl et de l'alfentanil ont été comparées par l'adminstration i.v. simultanée des deux agents, la mesure de leurs concentrations plasmatiques et l'analyse compartimentale. De plus, la liaison aux protéines plasmatiques, les coefficients de partition érythrocytes/plasma et heptane/eau ont été comparés. Il semble que l'alfentanil ait un volume apparent de distribution beaucoup plus faible, une clairance totale plus petite et une demi-vie terminale plasmatique plus courte. L'alfentanil a également une liaison aux protéines plasmatiques plus importante, mais, à l'inverse du fentanyl, il ne se lie pas aux érythrocytes. En conclusion, l'alfentanil s'accumule moins que le fentanyl, il a une clairance hépatique réduite et aura une cinétique non linéaire à très fortes doses. Un appendice décrit le protocole en détail.

## VERGLEICHENDE PHARMAKOKINETIK VON FENTANYL UND ALFENTANYL

### ZUSAMMENFASSUNG

Es wurde die Pharmakokinetik des Fentanyls und des Alfentanyls bei simultaner i.v. Applikation beider Pharmaka sowohl durch Messung der Plasmakonzentration als auch durch Untersuchung der Verteilung in den Kompartimenten verglichen. Zusätzlich wurden die Plasmaproteinbindung, das Verhältnis von Erythrozyten zur Plasma- und Heptan zur Wasser-Verteilung gemessen. Bei Alfentanyl fand sich ein offenbar viel kleineres Verteilungsvolumen, kleinere totale Clearance und kürzere Halbwertzeit im Plasma. Bei Alfentanyl fand sich auch eine größere Plasmaproteinbindung, aber im Gegensatz zu Fentanyl keine Bindung an Erythrozyten. Daraus wird geschlossen, daß Alfentanyl weniger kumuliert als Fentanyl, eine geringe Leberclearance besitzt und bei sehr hohen Dosen keine lineare Kinetik aufweist. Im Anhang wird der zum Modell passende Vorgang im Detail beschrieben.

## FARMACOCINETICA COMPARADA DEL FENTANILO Y DEL ALFENTANILO

### SUMARIO

Se comparó la farmacocinética del fentanilo y del alfentanilo mediante la administración i.v. simultánea de ambas drogas, medición de las concentraciones en el plasma y análisis sectorial. Además, se llevó a cabo una comparación de la ligación proteínica del plasma, de la relación erytrocito : plasma y heptano : agua. Se abservó que el alfentanilo tenía un volumen aparente de distribución mucho más pequeño, una depuración total menor y una vida media terminal más corta en el plasma. Asimismo, el alfentanilo demostró tener una mayor ligación proteínica del plasma, pero al contrario del fentanilo, no tenía ligación alguna a los eritrocitos. Se llega a la conclusión de que el alfentanilo es menos cumulativo que el fentanilo, tiene una depuración hepática restringida y demostrará una cinética no-linear en dosis muy altas. En un apéndice, se describe en detalle el procedimiento de adaptación del modelo.

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# KETAMINE AND E.E.G. SEIZURE WAVES: INTERACTION WITH ANTI-EPILEPTIC DRUGS

Y. KAYAMA

## SUMMARY

When unrestrained cats were injected with ketamine 2–6 mg kg$^{-1}$ i.v., anaesthesia was associated with seizure waves induced in the cortical e.e.g. After cats were pretreated with trimethadione 500 mg kg$^{-1}$ i.p., ketamine did not induce seizure waves. Pretreatment with diphenylhydantoin 25 or 100 mg kg$^{-1}$ i.p. slightly enhanced seizure waves following ketamine. In both situations the anaesthetic effect of ketamine remained unaffected.

Kayama and Iwama (1972) demonstrated in previous experiments that, when cats were anaesthetized with ketamine, seizure waves appeared in the cortical e.e.g. From the pattern of e.e.g. waves, they found the ketamine-induced seizure waves to be similar to those characteristic of petit mal seizures. We report how anti-epileptic drugs counteracted induction of seizure waves by ketamine.

## METHODS

Experiments were performed on five unrestrained cats with chronically implanted electrodes in the sensorimotor and visual cortices and in the optic chiasma. The cortical electrodes were small stainless steel bolts screwed to the skull and the chiasmatic electrodes were a pair of stainless steel wires glued together with tips separated by about 0.5 mm. The cat was placed in a box (60 × 60 × 50 cm) with an observation window through which the effects of ketamine and other drugs were observed. Cables from the input terminals of amplifiers and those from the output terminals of an electronic stimulator (constant voltage type) were led into the observation box and connected to the cortical and chiasmatic electrodes respectively. E.e.g. was recorded on paper and visual cortical evoked potentials, induced by electrical stimulation of the optic chiasma, were displayed on an oscilloscope screen and photographed. The optic chiasma was stimulated every 1.5 s by a square pulse of 0.05 ms duration with a submaximal intensity of less than 40 V.

Ketamine was administered i.v. through a thin polyethylene catheter implanted chronically in the superior vena cava via the jugular vein. In each cat, ketamine was administered in the smallest dose sufficient to cause seizure waves (range 2–6 mg kg$^{-1}$). The anti-epileptic drugs used were trimethadione (anti - petit mal agent) and diphenylhydantoin (anti - grand mal agent). Trimethadione was dissolved in distilled water at a concentration of 50–80 mg ml$^{-1}$ and administered in a dose of 500 mg kg$^{-1}$ (Everett and Richards, 1944). Diphenylhydantoin, dissolved at a concentration of 50 mg ml$^{-1}$ in a solvent containing 40% propyleneglycol and 10.5% ethanol, was given in a dose of 25 mg kg$^{-1}$ or 100 mg kg$^{-1}$ (Everett and Richards, 1944). Both drugs were administered i.p. The procedure was as follows:

(1) Control observations were made of the effects of ketamine on e.e.g. and behaviour.

(2) Five hours after procedure 1, trimethadione, diphenylhydantoin or the solvent of diphenylhydantoin was administered to observe the effects of these drugs on e.e.g. and behaviour.

(3) One hour after procedure 2, the second administration of ketamine was made in the same dose as in the first procedure. Compared with the findings after the first procedure, those after the third procedure were taken as showing modification, if any, of the effects of ketamine by the drugs used in the second procedure.

At least 6 days was allowed for recovery from the effects of trimethadione or diphenylhydantoin before a cat was used for further experiments.

## RESULTS

Changes in behaviour, e.e.g. and cortical evoked potentials after i.v. administration of ketamine were the same as those reported previously (Kayama and Iwama, 1972). Behaviourally, ketamine induced general immobility with occasional twitching move-

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ments of the vibrissae or ears. No responses were observed to painful stimuli (strong pinching of the tail or the hairless skin of the paws). The pupils were dilated with a fixed gaze. Cortical e.e.g. during ketamine anaesthesia was characterized by enhanced desynchronized waves in the background and bursts of rhythmic hypersynchronous slow waves or slow waves with sharp spikes which can be interpreted as seizure activity (Kayama and Iwama, 1972) (figs 1B and 2A).

Evoked potentials in the visual cortex induced by single shock stimulation of the optic chiasma (fig. 3) had the same configuration as those described by previous workers (Malis and Kruger, 1956). The first downward deflection is the presynaptic activity, while the other major deflections are produced by activation of postsynaptic structures (Widén and Ajmone Marsan, 1960). Ketamine itself enhanced every component of the evoked potential (fig. 3A, D). It was notable, however, that for a short while after administration of ketamine, the postsynaptic components of the evoked potential were sometimes almost abolished (record at 1 min after ketamine in fig. 3A, D). Hereafter, this phenomenon will be referred to as "blocking of evoked potential". One interpretation of this phenomenon is that the cortex is already very active, showing seizure waves, and cannot increase or modify its activity in response to stimulation of the optic chiasma (Kayama and Iwama, 1972).

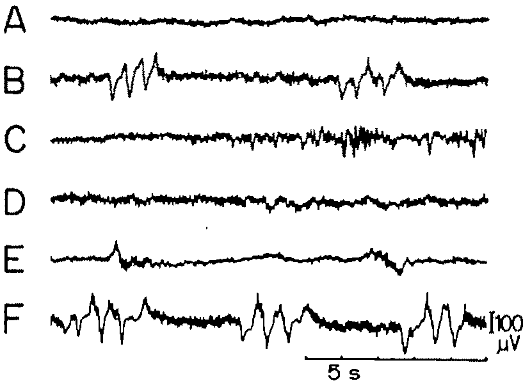

FIG. 1. E.e.g. effects of ketamine modified with trimethadione. All traces were recorded from the visual cortex. A = resting arousal state; B = 2 min after injection of ketamine 2.7 mg kg$^{-1}$; C = 59 min after injection of trimethadione 500 mg kg$^{-1}$; D = 2 min after injection of ketamine 2.7 mg kg$^{-1}$ performed soon after C; E = 2 min after injection of ketamine 5.4 mg kg$^{-1}$ performed 20 h after injection of trimethadione; F = 2 min after injection of ketamine 5.4 mg kg$^{-1}$ performed 7 days after injection of trimethadione.

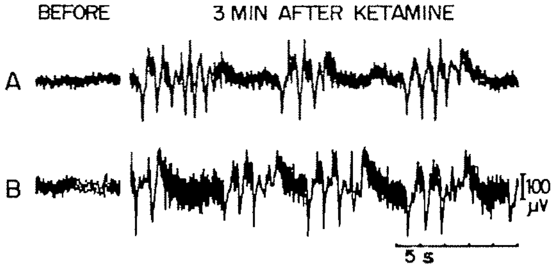

FIG. 2. E.e.g. effects of ketamine modified with diphenylhydantoin. E.e.g. records from the visual cortex recorded before and 3 min after injection of ketamine 3 mg kg$^{-1}$ are shown. A = before anti-epileptic treatment; B = 60 min after diphenylhydantoin 25 mg kg$^{-1}$.

The behavioural and e.e.g. changes caused by ketamine began to appear about 30 s after injection and were maximal between 1 and 3 min. All effects of ketamine disappeared after about 1 h and the second injection of the same dose of ketamine administered after 5 h had the same effects as the first one.

### *Interaction with trimethadione*

Interaction of ketamine with trimethadione was examined six times in four cats. Figure 1 shows typical records from one cat. In A and B, it was confirmed that ketamine 2.7 mg kg$^{-1}$, which was administered in the resting arousal state (A) slightly increased the amplitude of the desynchronized e.e.g., with occasional bursts of seizure waves (B). After the effects of ketamine disappeared completely, trimethadione was administered. Record C shows

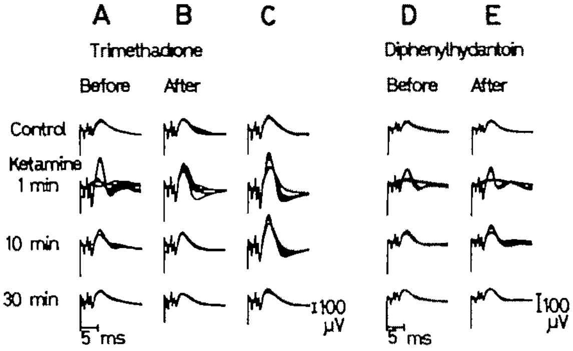

FIG. 3. Effects of ketamine on visual cortical evoked potentials induced by single shock stimulation of the optic chiasma. A = before trimethadione; B and C = 1 and 20 h after trimethadione, respectively; D and E = before and 1 h after diphenylhydantoin, respectively. Five to 10 traces were superposed in each record. A, B and C were obtained from the same cat as in figure 1. D and E were obtained from the same cat as in figure 2.

that with this drug no characteristic changes were induced in either the e.e.g. or behaviour. Although the cat sometimes fell into a drowsy state as indicated by spindles in the e.e.g., it was not possible to determine whether these effects could be ascribed to trimethadione. When the same dose of ketamine as in record B was injected 60 min after trimethadione, the desynchronized e.e.g. slightly increased in amplitude but no seizure waves were observed (D). The cat showed typical behavioural signs of ketamine anaesthesia at this time; it became immobile with dilated pupils and was unresponsive to painful stimulation. During this ketamine anaesthesia, enhancement of the evoked potential was observed (fig. 3B). Since in this case ketamine could not induce the seizure waves, the blocking of evoked potential was not encountered (the second record from the top in column B of fig. 3). During recovery from ketamine anaesthesia, ataxia was observed for a longer time than following ketamine alone.

Twenty hours after treatment with trimethadione, a double dose of ketamine ($5.4 mg kg^{-1}$) was tested. E.e.g. traces consisting of low voltage desynchronized waves with occasional slow undulations of the base line were observed (fig. 1E). Since no seizure waves were elicited, it was suggested that the effect of trimethadione had not disappeared. The evoked potentials were enhanced. Because of the absence of the seizure wave, it did not suffer any blocking in the stage of maximal enhancement (fig. 3C). With these electrographic signs, the cat was immobile and unresponsive to painful stimulation and its pupils dilated. Ataxia during recovery lasted more than 6 h. It was 7 days after the trimethadione injection that ketamine $5.4 mg kg^{-1}$ could induce typical e.e.g. changes (fig. 1F).

*Interaction with diphenylhydantoin*

Interaction of ketamine with diphenylhydantoin $25 mg kg^{-1}$ was examined in three cats. Essentially the same results were obtained. Records from one cat are shown in figure 2. After ketamine $3 mg kg^{-1}$ was found to anaesthetize the cat with induction of e.e.g. seizure waves (fig. 2A), diphenylhydantoin was injected. This treatment did not cause any marked behavioural and e.e.g. changes except for a slight increase in the amplitude of the desynchronized waves. Sixty minutes thereafter, the same dose of ketamine was injected (fig. 2B); seizure waves appeared in bursts at shorter intervals and desynchronized waves in the inter-burst intervals had greater amplitudes than in the control ketamine anaesthesia. Although in the ordinary condition the ketamine-induced seizure waves could not be found beyond 6 min after injection, this time was increased up to 9 min following pretreatment with diphenylhydantoin.

The facilitation of evoked potential following ketamine also took place in the diphenylhydantoin-treated condition (fig. 3E). The second record from the top of figure 3E shows that in the diphenylhydantoin-treated condition, the blocking of evoked potential sometimes took place in an early period after ketamine in the same way as in the untreated condition. This was because the seizure wave inducing effect of ketamine could not be antagonized by diphenylhydantoin.

Behaviourally, ketamine anaesthesia in the diphenylhydantoin-treated cats was not essentially different from that in the untreated cats.

While studying the blocking effect of diphenylhydantoin upon electrically induced generalized convulsion in rat, Everett and Richards (1944) noted that it became more obvious when the dose administered i.p. was increased from 25 to $135 mg kg^{-1}$. It was suspected therefore that, if administered in a considerably larger dose, diphenylhydantoin might antagonize the seizure-inducing effect of ketamine. Two cats received diphenylhydantoin $100 mg kg^{-1}$ followed by ketamine $5 mg kg^{-1}$; the e.e.g. after ketamine showed alternation of the strongly enhanced desynchronization and the spike and wave complex followed by electrical silence of 1–3 s duration. Thus, even diphenylhydantoin 100 $mg kg^{-1}$ failed to antagonize the seizure wave inducing effect of ketamine.

The solvent for diphenylhydantoin did not exert any marked effects on the ketamine-induced seizure activity.

## DISCUSSION

In a previous study using unrestrained cats, Kayama and Iwama (1972) found that, during ketamine anaesthesia, bursts of hypersynchronous slow waves were induced in the e.e.g. These slow waves were identified as seizure activity: (1) they were very rhythmic and appeared in various sites synchronously, (2) they were frequently accompanied by spikes, forming the spike and wave complex, and (3) there were many neurones the discharges of which were modified during the slow wave bursts in the same way as observed in experimental seizures (Kayama and Iwama, 1972). This finding has been confirmed by other workers who studied the effects of ketamine in chronically prepared, unrestrained cats (Mori et al., 1971; Winters et al., 1972; Wong and Jenkins, 1974). The present results are consistent with their observations. Some groups of workers reported that ketamine was unable to induce e.e.g. seizure activity (Miyasaka and Domino, 1968; Walter et al., 1972); Celesia and Chen, 1974). The reason for their failure would be that they used acute preparations under general anaesthesia or immobilized condition for testing the effects of ketamine.

Kayama and Iwama (1972) pointed out that the functional state of the brain produced by ketamine resembles petit mal epilepsy because the ketamine-induced seizure waves often took the form of spike and wave complexes and loss of consciousness was obtained without generalized convulsions. The present results lend support to this concept because the ketamine-induced seizure activity was found to be suppressed by an anti-petit mal drug, trimethadione.

In the present study, diphenylhydantoin did not suppress, and even enhanced, the seizure activity caused by ketamine. This is consistent with the concept that there is a resemblance between petit mal epilepsy and the functional state of the brain produced by ketamine because it is known that diphenylhydantoin is not effective in the treatment of petit mal epilepsy or may even worsen this type of seizure (Rall and Schleifer, 1980). Although diphenylhydantoin is used as an anti-epileptic drug, this drug is a central nervous stimulant which finally causes decerebrate rigidity (Rall and Schleifer, 1980). This effect may cause enhancement of seizure activity during ketamine anaesthesia.

In a previous paper, it was suggested that ketamine might interfere with consciousness, as does petit mal epilepsy, with an assumption that e.e.g. seizure activity would be essential for causing unconsciousness (Kayama and Iwama, 1972). This cannot be supported by the present study; although ketamine produced anaesthesia in cats after pretreatment with trimethadione, no seizure waves were observed in them. An explanation for unconsciousness during ketamine anaesthesia must be sought in a mechanism other than e.e.g. seizure waves.

Recently, it was reported that e.e.g. seizure activity was induced by intraventricularly administered encephalin, which is the natural ligand of the opiate receptor in the brain (Frenk, Urca and Liebeskind, 1978). During the encephalin-induced seizure activity, the animals were immobile, showing only occasional myoclonic jerks. The encephalin-induced e.e.g. seizure was suppressed by anti-petit mal drugs, not by anti-grand mal drugs (Snead and Bearden, 1980), which indicates that the seizure activity induced by ketamine and that by encephalin are similar. In addition, both ketamine and encephalin have strong analgesic effects. Since ketamine and encephalin have common effects upon the central nervous system, it is possible that at least part of the effect of ketamine on the central nervous system is exerted in close relation to the opiate receptor.

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## REFERENCES

Celesia, G. G., and Chen, R. -C. (1974). Effects of ketamine on EEG activity in cats and monkeys. *Electroenceph. Clin. Neurophysiol.*, **37**, 345.

Everett, G. M., and Richards, R. K. (1944). Comparative anticonvulsive action of 3,5,5-trimethyloxazolidine-2,4-dione (tridione), dilantin and phenobarbital. *J. Pharmacol. Exp. Ther.*, **81**, 402.

Frenk, H., Urca, G., and Liebeskind, J. C. (1978). Epileptic properties of leucine- and methionine-enkephalin: Comparison with morphine and reversibility by naloxone. *Brain Res.*, **147**, 327.

Kayama, Y., and Iwama, K. (1972). The EEG, evoked potential, and single unit activity during ketamine anesthesia in cats. *Anesthesiology*, **36**, 316.

Malis, L. I., and Kruger, L. (1956). Multiple response and excitability of the cat's visual cortex. *J. Neurophysiol.*, **19**, 172.

Miyasaka, M., and Domino, E. F. (1968). Neuronal mechanism of ketamine-induced anesthesia. *Int. J. Neuropharmacol.*, **7**, 557.

Mori, K., Kawamata, M., Mitani, H., Yamasaki, Y., and Fujita, M. (1971). A neurophysiologic study of ketamine anesthesia in the cat. *Anesthesiology*, **35**, 373.

Rall, T. W., and Schleifer, L. S. (1980). Drugs effective in the therapy of the epilepsies; in *The Pharmacological Basis of Therapeutics*, 6th edn (eds L. S. Goodman and A. Gilman), p. 448. New York: Macmillan.

Snead, O. C. III, and Bearden, L. J. (1980). Anticonvulsants specific for petit mal antagonize epileptogenic effect of leucine enkephalin. *Science*, **210**, 1031.

Walter, S., Arfel, G., de Pommery, J., Benhadji, M. F., and de Pommery, H. (1972). Ketamine—CI581: aspects electrophysiologiques. *Anesth. Analg. Réan.*, **29**, 197.

Widén, L., and Ajmone Marsan, C. (1960). Unitary analysis of the response elicited in the visual cortex of cat. *Arch. Ital. Biol.*, **98**, 248.

Winters, W. D., Ferrer-Allado, T., Guzman-Flores, C., and Alcaraz, M. (1972). The cataleptic state induced by ketamine;

A review of the neuropharmacology of anesthesia. *Neuropharmacology*, 11, 303.

Wong, D. H. W., and Jenkins, L. C. (1974). An experimental study of the mechanism of action of ketamine on the central nervous system. *Can. Anaesth. Soc. J.*, 21, 57.

## KETAMIN UND PAROXYSMALE EEG-TÄTIGKEIT: INTERAKTION MIT ANTIEPILEPTIKA

### ZUSAMMENFASSUNG

Nicht in ihrer Bewegungsfreiheit eingeschränkte Katzen, die 2 bis 6 mg kg$^{-1}$ Ketamin erhalten hatten, zeigten bei der Narkose paroxysmale Tätigkeiten im kortikalen EEG. Bei mit 500 mg kg$^{-1}$ Trimethadion vorbehandelten Katzen rief Ketamin keine Anfallstätigkeiten im EEG hervor. Vorbehandlung mit 25 oder 100 mg kg$^{-1}$ Diphenylhydantoin intraperitoneal hemmte leicht die auf Ketamin folgende Anfallstätigkeit. In beiden Fällen blieb die anästhetische Wirkung von Ketanest unbeeinflußt.

## QUETAMINA Y OLAS DE ATAQUES EN EL EEG: INTERACCION CON LAS DROGAS ANTIEPILEPTICAS

### SUMARIO

Cuando se inyectó 2–6 mg kg$^{-1}$ de quetamina i.v. a unos gatos libres, la anestesia se halló asociada a olas de ataques inducidos en el e.e.g. cortical. Cuando se administró previamente trimetadiona a los gatos en una dosis de 500 mg kg$^{-1}$ i.p., la quetamina no indujo olas de ataques. El pretratamiento con difenilhidantoina en dosis de 25 ó 100 mg kg$^{-1}$ i.p. realzó las olas de ataques consecutivas a la administración de quetamina. En ambas situaciones, el efecto anestético de la quetamina no sufrió alteración.

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# EXPERIMENTAL PORCINE MALIGNANT HYPERTHERMIA: THE ACTIVITY OF CERTAIN TRANSPORTING ENZYMES AND MYOFIBRILLAR CALCIUM-BINDING PROTEIN CONTENT IN THE MUSCLE FIBRE

I. NIEBRÓJ-DOBOSZ AND E. MAYZNER-ZAWADZKA

## SUMMARY

The activity of enzymes transporting calcium across the membrane of the muscle fibre and sarcoplasmic reticulum was studied. The activity of actomyosin $Mg^{2+}$-ATPase and the composition of troponin were investigated also. In seven Pietrain pigs halothane alone or with suxamethonium induced the malignant hyperthermia syndrome. In the animals with malignant hyperthermia $Ca^{2+}$-ATPase was not activated in the plasma membranes of the muscle fibres, when compared with control animals ($n = 4$). An increase of $Ca^{2+}$-ATPase of the sarcoplasmic reticulum was observed in animals with malignant hyperthermia; the opposite was noted in the control group. No significant changes in the activity of $Mg^{2+}$-ATPase of the sarcoplasmic reticulum and of $Mg^{2+}$-ATPase of actomyosin were observed after exposure to halothane in control pigs and those with malignant hyperthermia. The amount of troponin C was significantly changed in the animals with malignant hyperthermia. The mechanism of the development of malignant hyperthermia syndrome is discussed.

Malignant hyperthermia (MH), an abnormal response to certain anaesthetic agents, can occur in genetically susceptible strains of pig including the Pietrain strain. The acute clinical manifestations of this syndrome can be triggered by several potent inhalation anaesthetic agents and neuromuscular blocking drugs. Although, several years ago, mortality varied between 40% and 90% (Denborough et al., 1962; Britt, Locher and Kalow, 1969), more recently a figure of 28% has been reported (Britt, 1979).

Although the mechanism responsible for the development of MH has not been fully elucidated (see review by Hall, Lucke and Lister, 1980), it is postulated that the primary cause is a genetically determined defect in striated muscle, which may follow the administration of a number of potent anaesthetic or related agents. This defect seems to be connected, in some way, with disturbances in the transport and distribution of calcium ions in the muscle fibre. This assumption could explain the basic clinical manifestation of MH, such as the sudden increase in temperature, muscular rigidity and metabolic acidosis. There are, however, few data to support this hypothesis.

The present study investigated the activity of calcium-transporting enzymes in plasma membranes and sarcoplasmic reticulum of muscle fibres from pigs sensitive to anaesthetic agents. Our aim also was to study the action of actomyosin $Mg^{2+}$-ATPase, when stimulated by calcium ions, and to establish the composition of certain myofibrillar proteins, which exert a regulatory role in the contraction–relaxation cycle of the muscle.

## MATERIALS AND METHODS

### *Animals*

The investigations were carried out on muscle from 11 pigs of the pure Pietrain strain. No tests had been carried out previously on these animals to determine their sensitivity to anaesthetics. The age of the animals ranged from 10 weeks to 6.5 months and their weight from 16 to 92 kg. Animals were divided into positive or negative (control) to MH groups according to their reactions to triggering agents.

Anaesthesia was induced and maintained with thiopentone i.v. Following a control period several activating factors were applied in an attempt to trigger MH. These factors were: the administration of exogenous carbon dioxide or increasing the deadspace, the administration of halothane, and/or the administration of halothane plus carbon dioxide or increased deadspace, and/or the administration of halothane and suxamethonium (table I).

Measurements were made on arterial and venous

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TABLE I. *Sensitivity of pigs to agents provoking malignant hyperthermia*

| No. | Sensitivity to provoking agents | Hyper-capnia | Halo-thane | Halothane hypercapnia | Halothane + suxamethonium |
|---|---|---|---|---|---|
| 1 | + | + | | | |
| 2 | + | − | + | | |
| 3 | + | − | + | | |
| 4 | + | − | + | | |
| 5 | + | − | − | + | |
| 6 | + | − | − | − | + |
| 7 | + | − | − | − | + |
| 8 | − | − | − | − | − |
| 9 | − | − | − | − | − |
| 10 | − | − | − | − | − |
| 11 | − | − | − | − | − |

blood before and after introducing each new factor. Details of the anaesthetic procedure and the results of physiological, metabolic and hormonal changes are detailed elsewhere (Mayzner-Zawadzka, 1982; Mayzner-Zawadzka et al., 1982). The superficial and deep parts of the semitendinosus muscle (m.ST) of the hind limb were taken before the induction of anaesthesia. Similar specimens were taken from the contralateral hind limb at the peak of the malignant hyperthermia or at the end of the experiment.

*Biochemical techniques*

The semitendinosus muscle was divided into two parts which differed in the composition of their muscle fibres (Beermann et al., 1977). In the superficial part, type II fibres prevail, in the deep part type I fibres are more numerous.

The following investigations were carried out on this material:

(1) Determinations of the activity of $Ca^{2+}$-ATPase (EC 3.6.1.3.) in the plasma membranes of the skeletal muscle. The plasma membranes of the muscle fibre were prepared by the method of Schapira and colleagues (1974). The activity of $Ca^{2+}$-ATPase was determined in an incubation system consisting of calcium chloride 3 mmol $litre^{-1}$, EGTA 1 mmol $litre^{-1}$, ATP-Tris 1 mmol $litre^{-1}$, Tris 170 mmol $litre^{-1}$ (pH 7.2 unit) and plasma membranes protein 20–80 μg. After 30 min at 37°C the released inorganic phosphorus concentration was determined (Fiske and SubbaRow, 1925).

(2) Determination of total and $Mg^{2+}$-ATPase (EC 3.6.1.3.) activity in the sarcoplasmic reticulum. Sarcoplasmic reticulum was prepared by the method of Harigay, Ogawa and Sugita (1968). Total ATPase activity was determined in an incubation system of potassium chloride 100 mmol $litre^{-1}$, histidine 10 mmol $litre^{-1}$ (pH 7.2 unit), magnesium chloride 5 mmol $litre^{-1}$, ATP-Tris 5 mmol $litre^{-1}$, potassium oxalate 5 mmol $litre^{-1}$, calcium chloride 45 mmol $litre^{-1}$. $Mg^{2+}$-ATPase was determined in the above system with EGTA 500 mmol $litre^{-1}$ added, but without calcium. Fifty to 100 μg of sarcoplasmic reticulum protein was added to both. After 10 min at 25°C the concentration of inorganic phosphorus was determined (Fiske and SubbaRow, 1925). The activity of $Ca^{2+}$-ATPase was calculated as the difference between total ATPase and $Mg^{2+}$-ATPase.

(3) The activity of actomyosin $Mg^{2+}$-ATPase (EC 3.6.1.3.) was measured in myosin B which had been isolated as described by Furukawa and Peter (1971). The incubation system consisted of magnesium chloride 1 mmol litre $^{-1}$, Tris maleinate 20 mmol $litre^{-1}$ (pH 6.8 unit), potassium chloride 60 mmol litre $^{-1}$, ATP-Tris 1 mmol $litre^{-1}$ and myosin B 1 mg. After 10 min at 25°C the concentration of the released inorganic phosphorus was determined.

(4) The composition of troponin was investigated in an extract of myofibrillar proteins isolated from the muscle using the method of Furukawa, Sugita and Toyokura (1972). One hundred microgram of proteins was heated at 60 °C for 5 min in a system of phosphate buffer (pH 7.2 unit), dodecyl sulphate and beta-mercapto-ethanol. After 15 h at 25 °C electrophoresis in 10% polyacrylamide gel was performed (Weber and Osborn, 1969). The proteins were stained by Coomassie Blue R. The percent composition of the troponin components was determined by gel densitometry in an ERJ-65 densitometer (Zeiss, Jena). $R_F$ values of the proteins were determined by comparison with $R_F$ values of reference protein standards (Sigma).

The concentration of protein in plasma membrane, sarcoplasmic reticulum, myosin B and myofibrillar proteins preparation was determined as described by Lowry and colleagues (1951).

## RESULTS

In the group of pigs in which the MH syndrome failed to develop (control group) the activity of $Ca^{2+}$-ATPase in the plasma membranes of the muscle fibre increased significantly after the administration of the anaesthetic agents (table II), and this did not depend upon the type of muscle studied. In the animals in which the MH syndrome was induced the activity of $Ca^{2+}$-ATPase was not stimulated by the anaesthetic drugs.

No significant differences in the activity of $Mg^{2+}$-ATPase of the sarcoplasmic reticulum were observed before and after provocation in the control animals and those in which hyperthermia developed. At the end of the experiment the activity of this enzyme was increased in each muscle from both groups of animals, but the changes were not significant (table III). The anaesthetics inhibited the activity of $Ca^{2+}$–ATPase of the sarcoplasmic reticulum in the control group. In the animals with MH syndrome the activity of this enzyme was increased significantly (table III).

There was a modest increase in the actomyosin $Mg^{2+}$-ATPase, from the superficial part of m.ST in both groups when stimulated by calcium ions (table IV). The activity of this enzyme in the deep part of m.ST was increased, but not significantly, in

TABLE II. *$Ca^{2+}$-ATPase activity of the cell membrane of the skeletal muscle (nmol $P_i$ per mg protein per min) (mean ± SEM).* *$P < 0.02$*: difference in enzyme activity in the control group before and after activation*

| | Pars superficialis of m.ST | | Pars profunda of m.ST | |
|---|---|---|---|---|
| | Before activation | After activation | Before activation | After activation |
| Animals with MH ($n = 7$) | 0.90±0.18 | 1.08±0.21 | 0.50±0.15 | 1.11±0.29 |
| Control group ($n = 4$) | 0.67±0.02 | 1.57±0.27* | 0.92±0.22 | 2.24±0.22* |

TABLE III. *$Ca^{2+}$-ATPase and $Mg^{2+}$-ATPase activity in the sarcoplasmic reticulum of the skeletal muscle (nmol $P_i$ per mg protein per min) (mean ± SEM). Difference in enzyme activity in the group with MH before and after activation:* †$P < 0.025$; ‡$P < 0.05$

| | Pars superficialis of m.ST | | Pars profunda of m.ST | |
|---|---|---|---|---|
| | Before activation | After activation | Before activation | After activation |
| $Ca^{2+}$-ATPase | | | | |
| Animals with MH ($n = 7$) | 20.26±2.66 | 41.36±8.15‡ | 14.19±3.66 | 46.39±5.01† |
| Control group ($n = 4$) | 31.82±5.39 | 15.56±4.27 | 15.48±5.59 | 8.11±1.97 |
| $Mg^{2+}$-ATPase | | | | |
| Animals with MH ($n = 7$) | 13.29±3.94 | 16.57±3.57 | 12.50±2.52 | 33.97±9.95 |
| Control group ($n = 4$) | 14.71±2.27 | 24.28±2.70 | 12.28±5.52 | 28.35±11.98 |

TABLE IV. *Actomyosin $Mg^{2+}$-ATPase activity in the skeletal muscle (nmol $P_i$ per mg protein per min) (mean ± SEM)*

| | Pars superficialis of m.ST | | Pars profunda of m.ST | |
|---|---|---|---|---|
| | Before activation | after activation | Before activation | After activation |
| Animals with MH ($n = 7$) | 34.29±0.71 | 37.01±5.45 | 32.69±8.17 | 62.61±18.31 |
| Control group ($n = 4$) | 32.86±7.64 | 38.05±3.29 | 24.50±2.79 | 47.40±15.76 |
| + EGTA | | | | |
| Animals with MH ($n = 7$) | 10.47±2.27 | 4.95±1.47 | 7.66±3.00 | 20.19±6.66 |
| Control group ($n = 4$) | 4.87±0.35 | 2.86±0.49 | 10.21±2.25 | 18.06±4.02 |

both groups. The degree of the inhibition of the enzyme by EGTA was similar in both groups, but was more marked in the deep part of the muscle.

Significantly greater values of troponin C (TN-C) were found in the superficial part of m.ST in the animals with MH syndrome. In the deep part of the muscle of these animals TN-C concentration was significantly lower than in the control group (table V).

## DISCUSSION

The clinical manifestations of the malignant hyperthermia syndrome in pigs are basically similar to those observed in man. However, it is not known how far the data obtained in experimental hyperthermia can be related to those demonstrated in humans (Harrison et al., 1968; Berman et al., 1970; Denborough et al., 1971).

It is thought that an increase in the calcium concentration in the sarcoplasm of the muscle fibre is the cause of MH syndrome. The consequences of such an increase may be the activation of phosphorylase kinase and myosin ATPase, inhibition of troponin and uncoupling of oxidative phosphorylation. An increase in the concentration of calcium ions in muscle cell cytoplasm may be the consequence of the triggering action of anaesthetic agents on the cell membrane, sarcoplasmic reticulum and mitochondria. All these subcellular organelles have been implicated, but the experimental evidence is scant.

In the cell membrane of the muscle fibre, anaesthetic agents can activate calcium transport and increase the permeability of this membrane to extracellular calcium. The role of a defect in the muscle fibre cell membrane which leads to an increase in the intracellular calcium concentration remains hypothetical (Engel, 1977). It was postulated that plasmalemma is the site initially affected by anaesthetic agents (Gallant, Godt and Gronert, 1979). The barrier function of plasmalemma may be decreased or the action of the membrane Ca$^{2+}$-ATPase (McNamara, Sulakhe and Dhalla, 1971) may be ineffective, or both. No data have been presented to confirm this suggestion. The possible influence of a cell membrane defect on changes in intracellular calcium could be inferred indirectly from data demonstrating increased blood creatine kinase activity in MH syndrome in humans and animals (Isaacs and Barlow, 1970; Britt et al., 1973). Damage of cell membranes in MH may be suggested by the beneficial action of procaine or procainamide in human MH (Moulds and Denborough, 1972). Suxamethonium can provoke the development of MH syndrome in man and animals, and it is known to act on the cell membrane.

The anaesthetic agents exert various effects on the sarcoplasmic reticulum. They can cause activation of the normal processes responsible for the release of Ca$^{2+}$ from the sarcoplasmic reticulum, direct stimulation of Ca$^{2+}$ release and activation of Ca$^{2+}$ release with simultaneous impairment of calcium reaccumulation.

Most authors have implicated the sarcoplasmic reticulum in the primary aetiology of MH. This supposition is supported by Britt and colleagues (1973). Halothane in the concentrations used in general anaesthesia inhibits calcium uptake by the sarcoplasmic reticulum in MH patients. In healthy subjects Ca$^{2+}$ accumulation by sarcoplasmic reticulum (Kalow et al., 1970) was not affected by halothane and Ca$^{2+}$ uptake in some patients with MH was described as normal (Isaacs and Heffron, 1975; Isaacs, Heffron and Badenhorst, 1975), or less than normal. The activity of Ca$^{2+}$-ATPase in MH patients was decreased or normal (Isaacs and Heffron, 1975; Isaacs, Heffron and Badenhorst, 1975; Heffron and Isaacs, 1976). A normal Ca$^{2+}$ uptake: Ca$^{2+}$-ATPase ratio would suggest that in human MH the calcium transport between sarcoplasm and sarcoplasmic reticulum is unchanged.

TABLE V. *Troponin components of the skeletal muscle (%) (mean ± SEM).* ***$P < 0.001$*: difference in troponin C between the group with MH and the controls*

| | Animals with MH ($n = 7$) | | Control group ($n = 4$) | |
|---|---|---|---|---|
| | Pars superficialis | Pars profunda of m.ST | Pars superficialis | Pars profunda of m.ST |
| Troponin T | 60.11 ± 1.71 | 71.57 ± 3.82 | 61.09 ± 2.35 | 64.55 ± 6.76 |
| Troponin I | 24.52 ± 2.72 | 24.60 ± 3.64 | 28.95 ± 2.53 | 18.15 ± 4.22 |
| Troponin C | 15.41 ± 1.19*** | 3.83 ± 0.54*** | 9.93 ± 1.67 | 17.30 ± 3.49 |

Normal (Cheah and Cheah, 1978), moderately increased (Nelson et al., 1972; Berman and Kench, 1973; Steward and Thomas, 1973) or decreased (Denborough et al., 1971; Brücker et al., 1973) $Ca^{2+}$ uptake into porcine sarcoplasmic reticulum have been described. An abnormal function of sarcoplasmic reticulum in calcium binding has been demonstrated also in experimental MH (Nelson and Bee, 1979).

Although the problem of mitochondrial activity has been described (Cheah and Cheah, 1978), it has not been elucidated completely. A higher $Ca^{2+}$ efflux and smaller accumulation of $Ca^{2+}$ in MH-sensitive pigs at higher temperatures was observed. It was suggested also that the major action of anaesthetics on isolated human mitochondria in MH is an inhibition of electron transport with some uncoupling of oxidative phosphorylation (Britt et al., 1973).

It is difficult to indicate which of these mechanisms play the major roles in the maintenance of a sustained increase in the concentration of sarcoplasmic calcium in MH.

We believe that halothane affects the cell membrane of the muscle fibres and increases its permeability. Under normal conditions, owing to the action of $Ca^{2+}$-ATPase in the cell membrane, the correct calcium gradient is maintained. A failure of the activity of this enzyme in MH animals would be responsible for impaired extrusion of calcium from the cell. This could be a consequence of a defect in the cell membrane or of inhibition of the calcium pump by some extracellular or intracellular factors or both. In light of our investigations it seems that, under normal conditions, halothane inhibits moderately the active calcium transport into sarcoplasmic reticulum. In animals with MH a significant increase in $Ca^{2+}$-ATPase would indicate an increase in the calcium transport into the sarcoplasmic reticulum, which would be in agreement with the work of others (Nelson et al., 1972; Berman and Kench, 1973; Steward and Thomas, 1973). A slightly smaller calcium binding within the sarcoplasmic reticulum as a result of the action of halothane both in normal and MH pigs could be suggested by the increase in the activity of $Mg^{2+}$-ATPase. In the light of our investigations, as well as those of Isaacs and Heffron (1975) on malignant hyperthermia in humans, it may be assumed that changes in the activity of actomyosin $Mg^{2+}$-ATPase, when stimulated by calcium ions, are without any great significance in malignant hyperthermia syndrome. The abnormalities in the composition of troponin may be connected with disturbances in contraction–relaxation cycle in porcine malignant hyperthermia syndrome.

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### REFERENCES

Beermann, D. H., Cassens, R. G., Couch, C. C., and Nagle, F. J. (1977). The effects of experimental denervation and reinnervation on skeletal muscle type and intramuscular innervation. *J. Neurol. Sci.*, **31**, 207.

Berman, M. C., Harrison, G. G., Bull, A. B., and Kench, J. E. (1970). Changes underlying halothane-induced malignant hyperpyrexia in Landrace pigs. *Nature (Lond.)*, **225**, 653.

—— Kench, J. E. (1973). Biochemical features of malignant hyperthermia; in *International Symposium on Malignant Hyperthermia* (eds R. A. Gordon, B. A. Britt and W. Kalow), p. 287. Springfield, Ill.: C. C. Thomas.

Britt, B. A. (1979). Preface; in: *Malignant Hyperthermia* (ed. B. A. Britt). *Int. Anesthesiol. Clin.*, **17**, vii.

—— Kalow, W., Gordon, A., Humphrey, J. C., and Rewcastle, N. B. (1973). Malignant hyperthermia: an investigation of five patients. *Can. Anaesth. Soc. J.*, **20**, 431.

—— Locher, W. G., and Kalow, W. (1969). Hereditary aspects of malignant hyperthermia. *Can. Anaesth. Soc. J.*, **16**, 89.

Brücker, R. F., Williams, C., Popinigis, J., Galves, T. L., Vail, W. J., and Taylor, C. (1973). *In vitro* studies on liver mitochondria and skeletal sarcoplasmic reticulum fragments isolated from hyperpyrexic swine; in *International Symposium on Malignant Hyperthermia* (eds R. A. Gordon, B. A. Britt and W. Kalow), p. 238. Springfield, Ill.: C. C. Thomas.

Cheah, K. S., and Cheah, A. M. (1978). Calcium movements in skeletal muscle mitochondria of malignant hyperthermic pigs. *Febs Lett.*, **95**, 307.

Denborough, M. A., Forster, J. F. A., Lovell, R. R. H., Maplestone, F. A., and Villiers, J. D. (1962). Anaesthetic death in a family. *Br. J. Anaesth.*, **34**, 396.

—— Hird, F. J. R., King, J. O., Marginson, M. A., Mitchelson, K. R., Naylor, W. G., Rox, M. A. E., Zapf, P. W., and Condron, R. J. (1971). Mitochondrial and other studies in Australian Landrace pigs affected with malignant hyperthermia; in *International Symposium on Malignant Hyperthermia* (eds R. A. Gordon, B. A. Britt and W. Kalow), p. 229. Springfield, Ill.: C. C. Thomas.

Engel, W. K. (1977). Integrative histochemical approach to the defect of Duchenne muscular dystrophy; in *Pathogenesis of Human Muscular Dystrophies* (ed. L. P. Rowland), p. 277. Amsterdam, Oxford: Excerpta Medica.

Fiske, C., and SubbaRow, Y. (1925). The colorimetric determination of phosphorus. *J. Biol. Chem.*, **66**, 375.

Furukawa, T., and Peter, J. B. (1971). Troponin activity of different types of muscle fibres. *Exp. Neurol.*, **31**, 214.

—— Sugita, H., and Toyokura, Y. (1972). Comparative studies on myofibrillar proteins in different muscle fibres. *Exp. Neurol.*, **37**, 515.

Gallant, E. M., Godt, R. E., and Gronert, G. A. (1979). Role of plasma membrane defect of skeletal muscle in malignant hyperthermia. *Muscle Nerve*, **2**, 491.

Hall, G. M., Lucke, J. N., and Lister, D. (1980). Malignant hyperthermia—pearls out of swine? *Br. J. Anaesth.*, **52**, 165.

Harigay, C., Ogawa, Y., and Sugita, H. (1968). Calcium binding activity of microsomal fraction of rabbit red muscle. *J. Biochem. (Tokyo)*, **63**, 324.

Harrison, G. U., Biebuyck, J. F., Terblanche, J., Dent, D. M., Hickman, R., and Saunders, J. (1968). Hyperpyrexia during anaesthesia. *Br. Med. J.*, **3**, 594.

Heffron, J. J. A., and Isaacs, H. (1976). Malignant hyperthermia syndrome—evidence for denervation changes in human skeletal muscle. *Klin. Wochenschr.*, **54**, 865.

Isaacs, H., and Barlow, M. W. (1970). Malignant hyperpyrexia during anaesthesia: possible association with subclinical myopathy. *Br. Med. J.*, **1**, 275.

—— Heffron, J. J. A. (1975). Morphological and biochemical defects in muscles of human carriers of the malignant hyperthermia syndrome. *Br. J. Anaesth.*, **47**, 475.

—— —— Badenhorst, H. (1975). Predictive tests for malignant hyperpyrexia. *Br. J. Anaesth.*, **47**, 1075.

Kalow, W., Britt, B. A., Terreau, M. E., and Haist, C. (1970). Metabolic error of muscle metabolism after recovery from malignant hyperthermia. *Lancet*, **2**, 895.

Lowry, O. H., Rosebrough, N. J., Farr, A. L., and Randall, R. J. (1951). Protein measurement with the Folin phenol reagent. *J. Biol. Chem.*, **193**, 265.

McNamara, D. B., Sulakhe, P. V., and Dhalla, N. S. (1971). Properties of the sarcolemmal calcium ion-stimulated adenosine triphosphatase of hamster skeletal muscle. *Biochem. J.*, **125**, 525.

Mayzner-Zawadzka, E. (1982). Porcine malignant hyperthermia: possible role of hypoventilation and hypercapnia in development of MH. *Pol. Tyg. Lek.*, (in press).

—— Turlejska, E., Uścilko-Kaciuba, H., and Kwiatkowski, H. (1982). Porcine malignant hyperthermia: a possibility of prediction based on initial body temperature and blood measurements. *Anim. Production*, (in press).

Moulds, R. F. W., and Denborough, M. A. (1972). Procaine in malignant hyperpyrexia. *Br. Med. J.*, **4**, 526.

Nelson, T. E., and Bee, D. E. (1979). Temperature perturbation studies of sarcoplasmic reticulum from malignant hyperthermia pigs. *J. Clin. Invest.*, **64**, 895.

—— Jones, E. W., Venable, J. H., and Kerr, D. D. (1972). Malignant hyperthermia of Poland swine. *Anesthesiology*, **36**, 52.

Schapira, G., Niebrój-Dobosz, I., Piau, J.-P., and Delain, E. (1974). An improved technique for preparation of skeletal muscle cell plasma membrane. *Biochim. Biophys. Acta (Amst.)*, **345**, 348.

Steward, D. J., and Thomas, T. A. (1973). Intracellular calcium metabolism and malignant hyperpyrexia; in *International Symposium on Malignant Hyperthermia* (eds R. A. Gordon, B. A. Britt and W. Kalow), p. 409. Springfield, Ill.: C. C. Thomas.

Weber, K., and Osborn, M. (1969). The reliability of molecular weight determinations by dodecyl sulfate-polyacrylamide gel electrophoresis. *J. Biol. Chem.*, **244**, 4406.

## HYPERTHERMIE MALIGNE EXPERIMENTALE CHEZ LE PORC. ACTIVITE DE CERTAINES ENZYMES DE TRANSPORT ET CONTENU EN PROTEINE MYO-FIBRILLAIRE DE LIAISON DU CALCIUM DANS LA FIBRE MUSCULAIRE

### RESUME

L'activité de certaines enzymes de transport du calcium à travers la membrane de la fibre musculaire et le réticulum sarcoplasmique, a été étudiée ainsi que l'activité de l'actinomyosine $Mg^{++}$ ATPase et la composition de la troponine. Chez 7 porcs Pietrain, l'halothane seul ou associé à la succinylcholine induisit un syndrome d'hyperthermie maligne. Chez les animaux hyperthermiques, la $Ca^{++}$ ATPase n'était pas activée dans les membranes plasmatiques des fibres musculaires, par rapport aux contrôles ($n = 4$). Chez les animaux hyperthermiques, on a pu observer une augmentation de la $Ca^{++}$ ATPase de réticulum sarcoplasmique, à l'inverse de ce qui se passait dans le groupe témoin. L'exposition à l'halothane du groupe témoin et des porcs hyperthermiques n'a pas permis d'objectiver de modifications significatives dans l'activité de la $Mg^{++}$ ATPase du réticulm sarcoplasmique et de la $Mg^{++}$ ATPase de l'actomyosine. La quantité de troponine C était significativement différente chez les animaux hyperthermiques. Les mécanisme du développement du syndrome d'hyperthermie maligne est discuté.

## EXPERIMENTELL INDUZIERTE MALIGNE HYPERTHERMIE BEI SCHWEINEN. DIE AKTIVITÄTEN BESTIMMTER FÖRDERENZYME, UND DER MYOFIBRILLÖSE KALZIUMBINDENDE PROTEINGEHALT IN DEN MUSKELFASERN

### ZUSAMMENFASSUNG

Untersucht wurde die Aktivität der Enzyme, die Kalzium durch die Membranen der Muskelzellen und des sarkoplasmatischen Retikulums transportieren. Die Aktivität der Aktomyosins – $Mg^{2+}$-ATPase und die Zusammensetzung von Troponin wurden ebenfalls untersucht. Bei sieben Schweinen induzierte Halothan alleine oder mit Succinylcholin das Syndrom der malignen Hyperthermie. Bei den Tieren mit maligner Hyperthermie war die $Ca^{2+}$-ATPase in der Plasmamembran der Muskelzellen im Vergleich zu den kontrolltieren nicht aktiviert. Ein Anstieg der $Ca^{2+}$-ATPase des sarkoplasmatischen Retikulums war bei den Tieren mit maligner Hyperthermie zu beobachten. Das Gegenteil war in der Kontrollgruppe zu beobachten. Keine signifikante Veränderung in der $Mg^{2+}$-ATPase des sarkoplasmatischen Retikulums und der $Mg^{2+}$-ATPase des Aktomyosins war nach Halothanexposition bei den Kontrollschweinen und den Schweinen mit maligner Hyperthermie zu beobachten. Troponin C war bei den Tieren mit maligner Hyperthermie signifikant verändert. Es wird der Entstehungsmechanismus des Syndroms der malignen Hyperthermie diskutiert.

# HIPERTERMIA MALIGNA EXPERIMENTAL DEL CERDO: ACTIVIDAD DE ALGUNAS ENZIMAS TRANSPORTADORAS Y CONTENIDO DE PROTEINA LIGADORA DE CALCIO MIOFIBRILAR EN LA FIBRA MUSCULAR

## SUMARIO

Se estudió la actividad de las enzimas transportadoras de calcio a través de la membrana de la fibra muscular y del reticulo sarcoplásmico. También se investigó la actividad de la actomiosina $Mg^{2+}$-ATPase y la composición de la traponina. En siete cerdos de Pietrain, el halotano solo o con suxametonio indujo el síndrome de la hipertermia maligna. En los animales que pasdecían de hipertermia maligna, el $Ca^{2+}$-ATPase no se encontró activado en las membranes plásmicas de las fibras musculares, cuando se compararon con los amimales controles ($n = 4$). Se observó un aumento del $Ca^{2+}$-ATPase del retículo sarcoplásmico en los animales que padecían de hipertermia maligna; en el grupo control, se observó el contrario. No se notaron ningún cambio significante en la actividad del $Mg^{2+}$-ATPase del retículo sarcoplásmico ni del $Mg^{2+}$-ATPase de la actomiosina después de la exposición al halotano de los cerdos de control y de los que sufrían de hipertermia maligna. La cantidad de troponina varió de manera significativa en los animales con hipertermia maligna. Se trata del mecanismo de la evolución de la hipertermia maligna.

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# ALLERGY TO LOCAL ANAESTHESIA

M. McD. FISHER AND J. C. PENNINGTON

## SUMMARY

A 35-year-old female had severe anaphylactoid reactions to prilocaine and lignocaine on separate occasions. Intradermal testing was positive to serial dilutions of both drugs and negative to bupivacaine, which was subsequently used uneventfully. While intradermal testing for local anaesthetic allergy has limited application it would appear that when such tests are positive in high dilution they may discriminate between safe and unsafe anaesthetic agents.

The majority of patients with a history of allergy to local anaesthetic drugs are not allergic (de Shazo and Nelson, 1979) and true allergy, particularly to amide local anaesthetics, is rare. We report a patient with allergy to a number of local anaesthetic drugs in whom intradermal testing enabled subsequent regional anaesthesia to be administered with safety.

## CASE REPORT

The patient was a female born in 1946. She had a past history of eczema and allergy to shellfish, cosmetics and deodorants. During her first pregnancy in 1975 she attended a dental practitioner who performed an inferior dental block with 1% prilocaine with 1:100 000 adrenaline. Within 10 min of the injection her face became swollen bilaterally and she complained of faintness and breathlessness. No further details are available. Six months later while she was in labour a pudendal block was performed for forceps delivery with 1% xylocaine 20 ml. Within minutes the patient complained of feeling unwell and developed a generalized flushing with large weals and bronchospasm. Her face and conjunctiva became swollen. She was given hydrocortisone 100 mg, promethazine 50 mg i.v. and 1:1000 adrenaline 0.2 ml i.m. The bronchospasm and flushing settled, while oedema persisted for 12 h.

*Intradermal testing* was carried out in 1980 using 0.1-ml injections of dilutions of local anaesthetics in normal saline on the anterior aspect of the arm. The results are shown in table I. The testing was performed because the patient was 3 months pregnant and was concerned about local and regional anaesthesia.

In March, 1981 she underwent a normal confinement and an episiotomy was performed using 10 ml of 0.25% bupivacaine. There was no adverse response.

## DISCUSSION

There is considerable difficulty in verifying a history of local anaesthetic allergy. In a previous study Fisher (1979) noted that intradermal testing appeared useless in the assessment of anaphylactoid reactions to local anaesthetic drugs. These patients, however, had reactions confined to the skin and intradermal testing is not useful with any anaesthetic drug for reactions confined to skin (Fisher, 1981).

Intradermal testing has been used by others in the diagnosis of anaphylactoid reactions to local anaesthetics (Aldrete and Johnson, 1970; Incaudo et al., 1978; de Shazo and Nelson, 1979). False positives, possibly related to paraben, appear to be the major disadvantage although there is a high correlation with drug reactions with dilutions of more than 1:1000 (Incaudo et al., 1978; de Shazo and Nelson,

TABLE I. *Intradermal testing in a patient after severe anaphylactoid reactions to local anaesthetic. Expressed as weal size over flare size (mm). NT = not tested*

| | Dilution | | | |
|---|---|---|---|---|
| Drug | 1:10 000 | 1:1 000 | 1:100 | 1:10 |
| 1% Procaine | NT | NT | — | 0/8 |
| 1% Xylocaine | 14/40 | 14/40 | NT | NT |
| 1% Mepivacaine | 0/0 | 0/0 | 0/0 | 0/0 |
| 1% Bupivacaine | 0/0 | 0/0 | 0/0 | 0/0 |
| 0.5% Amethocaine | 5/15 | 12/28 | NT | NT |
| 1% Prilocaine | 10/45 | 15/45 | NT | NT |

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1979). Severe systemic reaction has been described with 1:10 dilution (Mulvey, 1980). Progressive challenge has also been used to exclude and confirm the history (Incaudo et al., 1978; de Shazo and Nelson, 1979; Brown, Beamish and Wildsmith, 1981).

In this patient we found positive weal and flare reactions at high dilutions to the two drugs reacted to (lignocaine and prilocaine) and to tetracaine. A drug with negative skin tests (bupivacaine) was used uneventfully. Four patients in the series reported by Incaudo and colleagues (1978) reacted to more than one drug in high dilution and the drugs came from both amide and ester groups. Reddrop and Lilley (1980) emphasized that tests for one group give no information about the other, and both groups should be tested. It appears from the case under discussion that when positive weal and flare reactions to local anaesthetics occur in high dilution, the tests should be repeated with alternative local anaesthetics from both groups. Local anaesthetics with negative intradermal tests may be safe alternatives to those with positive tests in high dilution.

### REFERENCES

Aldrete, J. A., and Johnson, D. A. (1970). Evaluation of intracutaneous testing for investigation of allergy to local anesthetics. *Anesth. Analg. (Cleve.)*, 49, 173.

Brown, D. T., Beamish, D., and Wildsmith, J. (1981). Allergic reaction to an amide local anaesthetic. *Br. J. Anaesth.*, 53, 455.

Fisher, M. McD. (1979). Intradermal testing in the diagnosis of acute anaphylaxis during anaesthesia—results of five years experience. *Anaesth. Intens. Care*, 7, 58.

——(1981). The diagnosis of acute anaphylactoid reactions to anaesthetic drugs. *Anaesth. Intens. Care*, 9, 235.

Incaudo, G., Schatz, M., Patterson, R., Rosenberg, M., Yammamoto, F., and Hamburger, R. N. (1978). Administration of local anaesthetics to patients with a history of a prior adverse reaction. *J. Allerg. Clin. Immunol.*, 6, 339.

Mulvey, P. (1980). Allergy to local anaesthetics. *Med. J. Aust.*, 1, 386.

Reddrop, C., and Lilley, J. (1980). Allergy to local anaesthetics. *Med. J. Aust.*, 11, 634.

de Shazo R. D., and Nelson, H. S. (1979). An approach to the patient with a history of local anaesthetic hypersensitivity: experience with 90 patients. *J. Allerg. Clin. Immunol.*, 63, 387.

## ALLERGIE A L'ANESTHESIE LOCALE

### RESUME

Une femme de 35 ans a eu à plusieurs reprises de sërieuse réactions anaphylactoïdes à la prilocaïne et à la lignocaïne. Les tests intradermiques ont été positifs aux dilutions en séries de ces deux médicaments et négatifs à la bupivacaïne que l'on a utilisée par la suite sans aucun inconvénient. Bien que les tests intradermiques pour déterminer les allergies aux anesthésiants locaux aient des applications limitées, il semblerait que lorsque ces tests sont positifs aux dilutions fortes ils permettent de distinguer les agents anesthésiants sûrs de ceux qui ne le sont pas.

## ALLERGIE AUF LOKALANÄSTHETIKA

### ZUSAMMENFASSUNG

Eine 35 Jahre alte Frau reagierte mit schwerer anaphylaktoider Reaktion auf Prilokain und Lidokain bei verschiedenen Gelegenheiten. Der intradermale Test war positiv auf Reihenverdünnungen beider Substanzen und negativ auf Bupivacain, das anschließend ohne Folgen verwendet wurde. Während die Brauchbarkeit des intradermalen Allergietestes auf Lokalanästhetika eingeschränkt ist, scheint es, daß man bei positivem Testergebnis in hoher Verdünnung zwischen sicherem und unsicherem Anästhetikum unterscheiden kann.

## ALERGIA A LA ANESTESIA LOCAL

### SUMARIO

Una paciente de 35 años de edad presentó agudas reacciones anafilactoideas a la prilocaína y a la lignocaína en diferentes ocasiones. La prueba intradermal fue positiva ante disoluciones seriales de ambas drogas y negativa ante la bupivacaína, que se usó posteriormente si éxito alguno. Aunque la prueba intradermal relativa a la alergia a la anestesia local tiene una aplicación limitada, parece ser que cuando tales pruebas son positivas en grandes disoluciones, puede que discriminen entre los agentes anestésicos seguros y peligrosos.

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# CONTROLLED HYPOTENSION TO MINIMIZE BLOOD LOSS OF ANAEMIC JEHOVAH'S WITNESS PATIENT UNDERGOING TOTAL HIP AND SHOULDER REPLACEMENT

A. J. A. CUNNINGHAM

## SUMMARY

A Jehovah's Witness with disabling rheumatoid arthritis, and a normocytic, normochromic anaemia, underwent on separate occasions a staged total hip and a shoulder replacement. Controlled hypotension with therapeutic doses of sodium nitroprusside was used to minimize blood loss, and haemodilution with crystalloid fluids was used to maintain normal cardiac output.

Induced or controlled hypotension was introduced in the 1950's to produce optimal operating conditions during plastic surgery (Enderby, 1961) and certain neurosurgical procedures (Aserman, 1953) and subsequently to decrease intraoperative blood loss during major surgical procedures (Larson, 1964). Sodium nitroprusside has established itself as the agent of choice for controlled hypotension dur-

loss during major surgical procedures (Larson, 1964). Sodium nitroprusside has established itself as the agent of choice for controlled hypotension dur-

potency and low frequency of tachyphylaxis, and its low toxic:therapeutic ratio (Palmer and Lasseter, 1975). Pre-existing anaemia is considered a contraindication to controlled hypotension because of the decrease in arterial oxygen carrying capacity (Lindop, 1975) but this case report illustrates the successful use of haemodilution with crystalloid fluids, and controlled hypotension to minimize blood loss, to undertake staged hip and shoulder replacement in an anaemic Jehovah's Witness.

## CASE REPORT

A 52-yr-old female Jehovah's Witness was admitted for elective total hip replacement in May 1980. She had a 17-yr history of progressively disabling rheumatoid arthritis involving her wrists, shoulder, hips and knees.

In 1978 the patient underwent successful bilateral total knee replacement, blood loss being controlled by a tourniquet. She had no symptoms or signs of cerebrovascular disease, ischaemic heart disease, pulmonary or renal disease. She had a normocytic, normochromic anaemia (haemoglobin 9.6 gm $dl^{-1}$) which was unresponsive to oral iron therapy, secondary to the chronic rheumatoid disease. A devout Jehovah's Witness, she refused transfusion of homologous blood or any blood products and she also declined autologous blood transfusion. Her entrophen and indomethacin medication was discontinued 1 week before operation. Coagulation screen, bleeding time and platelet count were normal.

### *Anaesthetic technique*

#### *Procedure 1: total hip replacement*

The patient weighed 60 kg and received diazepam 10 mg by mouth 90 min before surgery. Anaesthesia was induced with sodium thiopentone 5 mg $kg^{-1}$ and suxamethonium 1 mg $kg^{-1}$ was given i.v. to facilitate endotracheal intubation. Ventilation was controlled using a Bain non-rebreathing system (tidal volume 12 ml $kg^{-1}$ and respiratory rate 12 b.p.m). Anaesthesia was maintained with nitrous oxide 4 litre in oxygen 2 litre $min^{-1}$ and morphine i.v. Pancuronium i.v. was used to maintain neuromuscular blockade.

An intra-arterial cannula was inserted to the radial artery to permit the continuous measurement of arterial pressure and blood sampling for blood-gas analysis. Central venous pressure (c.v.p.) was monitored via the right internal jugular vein and the electrocardiogram (e.c.g.) (V5 lead position) displayed on an oscilloscope. An indwelling Foley catheter, and an oesophageal stethoscope and temperature probe were inserted.

Baseline arterial pressure was 130/90 mm Hg and c.v.p. 8 cm $H_2O$. Sodium nitroprusside solution

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0.01% (50 mg in 500 ml of 5% dextrose in water solution) was infused through a separate i.v. line via an Imed infusion pump. A rate of 1–3 $\mu$g kg$^{-1}$ min$^{-1}$ was used to maintain a mean arterial pressure of 70 mm Hg from skin incision to surgical closure. The total dose of sodium nitroprusside infused was 8 mg (80 ml of 0.01% solution) or 0.13 mg/kg body weight. To prevent wide fluctuations in arterial pressure, 0.5% halothane was occasionally added to the inspired gas mixture. Arterial blood-gas analysis was performed every 30 min to assess acid–base status and adequacy of ventilation. With a $F\text{I}_{O_2}$ 0.33, $Pa_{O_2}$ values ranging from 13.7 to 17.3 kPa were recorded while $Pa_{CO_2}$ and $HCO_3$- ranged from 3.7 to 4.0 kPa and 22–24 mmol litre$^{-1}$ respectively.

Lactated Ringer's solution was infused at a rate of 10–15 ml h$^{-1}$ per kg to maintain c.v.p. 8–12 cm $H_2O$ and to ensure a urine output greater than 1 ml h$^{-1}$ per kg. Operative blood loss was assessed by weighing sponges, measuring suction drainage, and estimating blood loss on drapes. During the 2.5-h procedure, the estimated intraoperative blood loss was 600 ml. A total of 3800 ml of crystalloid fluid was infused. Following the withdrawal of sodium nitroprusside the patient became, and remained, normotensive.

The postoperative course was uneventful although haemoglobin decreased to 6.9 gm dl$^{-1}$ on the 2nd day after operation. Before discharge, haemoglobin had increased to 8.1 gm dl$^{-1}$.

*Procedure 2: total shoulder replacement*

The patient was readmitted in November 1980 for elective total shoulder replacement. She had been taking oral iron for 6 months following her total hip replacement and, on admission, haemoglobin was 9.9 gm dl$^{-1}$ (a normocytic normochromic anaemia). A similar anaesthetic technique was used: haemodilution with lactated Ringer's solution at 10–15 ml h$^{-1}$ per kg with c.v.p. monitoring and controlled hypotension using 0.01% sodium nitroprusside solution to maintain a mean arterial pressure of 70 mm Hg. The total dose of sodium nitroprusside infused was 10 mg (102 ml of 0.01% solution) or 0.16 mg kg$^{-1}$ body weight. Arterial blood-gas analyses were performed every 30 min during controlled hypotension to assure $Pa_{O_2} > 13.3$ kPa, adequate pulmonary ventilation and to detect unexplained metabolic acidosis. Blood loss was estimated as 900 ml during an otherwise uneventful 4-h procedure. Recovery was uneventful and on oral iron medication haemoglobin was 7.6 gm dl$^{-1}$ before discharge.

## DISCUSSION

Published reports of average blood loss for total hip replacement have ranged from 1086 ml (Sculco and Ranawat, 1975) to 2250 ml (Davis, Jennings and Harris, 1974). The use of controlled hypotension to decrease intraoperative blood loss during total hip replacement is established. Thompson and colleagues (1978) showed a decrease in blood loss from 1183 ml (±172) in normotensive patients to 326 ml (±41) in a group of patients subjected to controlled hypotension with nitroprusside. Vazeery and Lunde (1979) reported a mean blood loss of 212 ml in a hypotensive group compared with 1038 ml in normotensive controls. The combination of surgical expertise in securing haemostasis and sodium nitroprusside-induced hypotension resulted in blood losses of 600 and 900 ml during the two major orthopaedic procedures described above.

Despite the reported benefits of decreases in blood loss, decreases in the number of blood transfusions and shorter operating time, controversy concerning the use of controlled hypotension for surgical procedures has persisted for many years. Reports have been published recently concerning the safety of controlled hypotension for total hip replacement. No untoward effects from hypotension induced with sodium nitroprusside were noted on postoperative brain, liver or kidney function in patients undergoing total hip replacement while alveolar gas exchange and myocardial function were preserved (Thompson et al., 1978). Cardiac index increased by 20% in patients treated with sodium nitroprusside and undergoing total hip replacement (Lawson et al., 1976). The increase in cardiac output was achieved through decreased peripheral vascular resistance, with only minor changes in heart rate. Acid–base status was normal, as was urine output, during the period of hypotension.

Sodium nitroprusside was chosen as the hypotensive agent for these orthopaedic procedures because of its rapid onset of action, its rapid reversibility, its high potency, its specific action on arteriolar vessels and its lack of effect on cardiac and other smooth muscle (Palmer and Lasseter, 1975). Sodium nitroprusside maintains a stable cardiac output and cerebral blood flow by producing a proportional decrease in perfusion pressure and peripheral vascular resistance (Stoyka and Schutz, 1975).

The major concern relating to sodium nitroprusside is the danger of cyanide (CN) toxicity. Nitroprusside is metabolized into cyanide via a direct non-enzymatic reaction with oxyhaemoglobin and the resulting cyanide is detoxified by the hepatic rhodanase system to thiocyanate with the aid of thiosulphate (Tinker and Michenfelder, 1976). Avoidance of cyanide toxicity is a matter of strict adherence to dosage limits. Patients can tolerate up to $8\,\mu g\,kg^{-1}\,min^{-1}$ or $0.5\,mg\,h^{-1}$ per kg without evidence of cyanide toxicity for up to 48 h (Michenfelder and Tinker, 1977) and so far there have been no clinical or experimental reports of cyanide toxicity when the dose of sodium nitroprusside infused was less than $8\,\mu g\,kg^{-1}\,h^{-1}$.

In the two procedures reported here, sodium nitroprusside was infused via a separate i.v. cannula and a calibrated infusion pump maintained a dosage of $1-3\,\mu g\,kg^{-1}\,min^{-1}$. No tachyphylaxis developed during the infusion and arterial blood-gas analyses did not show evidence of unexplained metabolic acidosis, an early indication of toxicity (Greiss, Tremblay and Davies, 1976).

The total dose of sodium nitroprusside infused during the total knee replacement was 8 mg ($0.13\,mg\,kg^{-1}$) and during the total shoulder replacement 10 mg ($0.16\,mg\,kg^{-1}$). These total doses were considerably less than the $0.6$-$mg\,kg^{-1}\,h^{-1}$ dose (Du Cailar et al., 1978) or the $1.5$-$mg\,kg^{-1}$ dose recommended for short-term infusions (Vesey, Cole and Simpson, 1976). Serum cyanide concentrations were not measured in these two orthopaedic operations because of the small therapeutic dose of nitroprusside used and because no untoward effects followed the infusion.

Pre-existing anaemia is considered a relative contraindication to the use of induced hypotension because of its effect of decreasing arterial oxygen content. Since sodium nitroprusside produces a proportional decrease in perfusion pressure and peripheral vascular resistance (Stoyka and Schutz, 1975) tissue blood flow remains unchanged. Thus, provided arterial oxygen saturation is maintained and haemoglobin concentration is not markedly decreased, the available tissue oxygen should be sufficient to maintain normal cellular function.

The use of a triple-lumen, flow-directed Swan–Ganz catheter to measure cardiac output during surgery in association with the controlled hypotension would have been advantageous and had the patient had evidence of ischaemic or valvular heart disease, or of chronic obstructive lung disease, a Swan–Ganz catheter would have been inserted. As the patient had no cardiac or pulmonary disease, changes in central venous pressure would reasonably reflect changes in cardiac preload and would guide i.v. fluid requirement.

The case presented illustrates that major surgery can be safely perfomed on an anaemic patient (haemoglobin $< 10\,gm\,dl^{-1}$) using haemodilution to maintain normal cardiac output and controlled hypotension to minimize blood loss.

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REFERENCES

Aserman, D. (1953). Controlled hypotension in neurosurgery with hexamethonium bromide and procaine amide. *Br. Med. J.*, **1**, 961.

Davis, N. J., Jennings, J. J., and Harris, W. H. (1974). Induced hypotension anaesthesia for total hip replacement. *Clin. Orthoped.*, **101**, 93.

Du Cailar, J., Mathiew Daude, J. C., Deschodt, J., Lamarche, Y., and Castel, C. (1978). Nitroprusside, its metabolites and red cell function. *Can. Anaesth. Soc. J.*, **25**, 92.

Enderby, G. E. (1961). Hypotensive anaesthesia in plastic surgery. *Br. J. Plast. Surg.*, **14**, 41.

Greiss, L. Tremblay, N. A. G., and Davies, D. W. (1976). The toxicity of sodium nitroprusside. *Can. Anaesth. Soc. J.*, **23**, 480.

Larson, A. G. (1964). Deliberate hypotension. *Anesthesiology*, **25**, 682.

Lawson, N. W., Thompson, D. S., Nelson, C. L., Flacke, J. W., and North, R. E. (1976). Sodium nitroprusside-induced hypotension for supine total hip replacement. *Anesth. Analg. (Cleve.)*, **55**, 654.

Lindop, M. J. (1975). Complications and morbidity of controlled hypotension. *Br. J. Anaesth.*, **47**, 799.

Palmer, R., and Lasseter, K. (1975). Sodium nitroprusside. *N. Engl. J. Med.*, **292**, 294.

Michenfelder, J. D., and Tinker, J. H. (1977). Cyanide toxicity and thiosulphate protection during chronic administration of sodium nitroprusside in the dog: correlation with human case. *Anesthesiology*, **47**, 441.

Sculco, T. P., and Ranawat, C. (1975). The use of spinal anaesthesia for total hip replacement arthroplasty. *J. Bone Joint Surg.*, **57**, 173.

Stoyka, W. W., and Schutz, H. (1975). The cerebral response to sodium nitroprusside and trimethaphan controlled hypotension. *Can. Anaesth. Soc. J.*, **22**, 275.

Thompson, G. E., Miller, R. D., Stevens, W. C., and Murray, W. R. (1978). Hypotensive anaesthesia for total hip arthroplasty: a study of blood loss and organ function (brain, heart, liver and kidney). *Anesthesiology*, **48**, 91.

Tinker, J. H., and Michenfelder, J. D. (1976). Sodium nitroprusside: pharmacology, toxicology and therapeutics. *Anesthesiology*, **45**, 340.

Vazeery, A. K., and Lunde, O. (1979). Controlled hypotension in hip joint surgery. *Acta Orthop. Scand.*, **50**, 433.

Vesey, C. J., Cole, P. V., and Simpson, P. J. (1976). Cyanide and thiocyanate concentrations following nitroprusside infusion in man. *Br. J. Anaesth.*, **48**, 651.

## HYPOTENSION CONTROLEE POUR LIMITER LES PERTES SANGUINES CHEZ UN TEMOIN DE JEHOVAH ANEMIQUE DEVANT SUBIR UNE PROTHESE TOTALE DE HANCHE ET D'EPAULE

### RESUME

Un Témoin de Jehovah, porteur d'une polyarthrite rhümatoïde invalidante et d'une anémie normochrome, normocytaire, a subi de façon séparée les poses de prothèses totales de hanche et d'épaule règlées. Une hypotension contrôlée avec des doses thérapeutiques de nitroprussiate de sodium a été utilisée pour minimiser le saignement et une hémodilution avec des solutés cristalloïdes a été utilisée pour préserver un débit cardiaque normal.

## KONTROLLIERTE HYPOTENSION ZUR VERRINGERUNG DES BLUTVERLUSTES BEI EINEM ANÄMISCHEN ZEUGEN-JEHOVA-PATIENTEN, DER SICH EINER TOTALEN HÜFT- UND SCHULTERENDOPROTHESE-OPERATION UNTERZIEHEN MUßTE

### ZUSAMMENFASSUNG

Ein Zeuge Jehovas mit versteifender, rheumatoider Arthritis und einer normozytären, normochromen Anämie, unterzog sich einem mehrzeitigen, totalen Hüft- und Schultergelenksersatz. Kontrollierte Blutdrucksenkung mit therapeutischen Dosen von Natriumnitroprussid wurde verwendet, um den Blutverlust so niedrig wie möglich zu halten und eine Hämodilution mit kristalloiden Lösungen diente dazu, ein normales Herzminutenvolumen aufrecht zu erhalten.

## HIPOTENSION CONTROLADA PARA REDUCIR A UN MINIMO LA PERDIDA DE SANGRE EN UN TESTIGO DE JEHOVA ANEMICO SOMETIDO A REEMPLAZAMIENTO TOTAL DE CADERA Y HOMBRO

### SUMARIO

Un testigo de Jehová que presentaba artritis reumatoide incapacitadora y una anemia normocrónica de carácter normocítico, fue sometido en diversas ocasiones al reemplazamiento total de cadera y hombro lo cual se efectúo en varias fases. Se uso hipotensión controlada con dosis terapéuticas de nitroprusiato de sodio para reducir a un mínimo la pérdida de sangre, usándose una hemodilución conflúidos cristaloides para mantener el ritmo cardiaco normal.

*Br. J. Anaesth.* (1982), 54, 899

# CORRESPONDENCE

### β-BLOCKING DRUGS AND THE LOWER OESOPHAGEAL SPHINCTER

Sir,—Regurgitation occuring during surgery is a major cause of anaesthetic-related morbidity and mortality and therefore in the past few years there has been great interest in the effects of drugs used during anaesthesia on the lower oesophageal sphincter (LOS).

Patients commonly present for surgery on long-term oral $\beta$-adrenoceptor blocking therapy for the treatment of hypertension and ischaemic heart disease. In addition these drugs are frequently used i.v. to attenuate the sympathetic response to laryngoscopy and tracheal intubation (Coleman and Jordan, 1980) and to protect against various arrythmias associated with surgery (Rollason and Russell, 1980; Whitehead, Whitmarsh and Horton, 1980).

Previous studies of the effects of $\beta$-adrenoceptor active drugs on the LOS have been confined to the opossum (an animal with a distal oesophageal smooth muscle similar to that in man). With this preparation it has been demonstrated that $\beta$-adrenoceptor stimulation reduces the tone of the LOS and it was suggested that this effect was probably mediated via $\beta_2$ receptors (DiMarino and Cohen, 1975).

We studied the effect of low-dose $\beta$-adrenoceptor blocking drugs in man. We have examined the effects of three drugs used commonly during anaesthesia by the i.v. route in doses up to 2 mg, which represent approximately equipotent chronotropic blocking dose of propranolol, metoprolol and oxprenolol (Weiner, 1980). This study was undertaken on 10 healthy volunteers who received on three separate occasions one of these three drugs in two increments of 1 mg i.v. The experiment was conducted on a random, subject-blind basis using the same technique and methods described in a recent communication (Cotton, Smith and Fell, 1981).

Assessment of the results by analysis of variance revealed that there was a significant increase in both LOS and barrier pressures (LOS minus gastric pressure) in response to metoprolol ($f = 2.82$), but not in response to either oxprenolol ($f = 0.76$) or propranolol ($f = 1.48$) (fig. 1). The increase in barrier pressure was not significant 5 min after the second injection of metoprolol, but was significant throughout the subsequent measurements.

Metroprolol is generally regarded as a cardioselective $\beta$-adrenoceptor blocking drug with action predominantly on $\beta_1$ receptors in low doses, although some degree of $\beta_2$ receptor blockade occurs at higher doses as with all cardioselective $\beta$-adrenoceptor blockers. However, oxprenolol possesses both $\beta_1$- and $\beta_2$-blocking effects and exhibits intrinsic sympathomimetic activity (ISA), whereas propranolol is both a $\beta_1$- and $\beta_2$-adrenoceptor blocker with no ISA. The doses of drugs used were selected as being *approximately* equipotent in terms of chronotropic blockade (Weiner, 1980) and also these conform to the doses used i.v. for clinical purposes (Colemen and Jordan, 1980; Rollason and Russell, 1980; Whitehead, Whitmarsh and Horton, 1980).

The positive response only to metoprolol provoked the interesting speculation that the human LOS may respond to $\beta_1$ agonists, unlike the opossum in which the LOS probably contains $\beta_2$ receptors (DiMarino and Cohen, 1975). Alternatively, it is also likely that failure to demonstrate a significant increase with the other two drugs results from lack of equipotent activity on the LOS $\beta$ receptors.

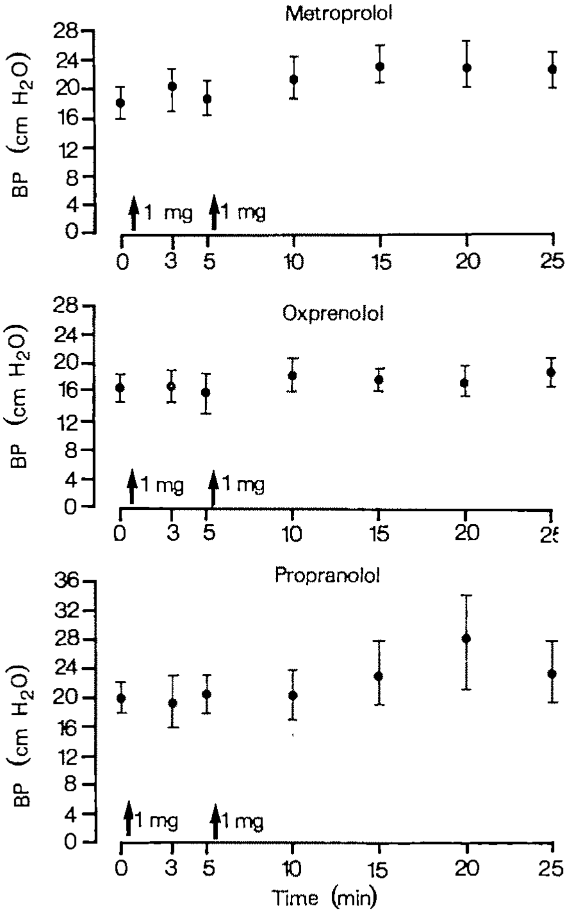

FIG. 1. effect of metoprolol, oxprenolol and propranolol on barrier pressure (BP). Mean ± SEM. At each arrow 1 mg of the respective drug was given.

It is unlikely that the response to metoprolol represents a random temporal increase in barrier pressure, as extensive studies in our department suggest that, although there may be random increases in gastric pressure, there is an accompanying increase in LOS pressure. This could be predicted from the "adaptive response" of the LOS whereby increase of gastric pressure produces a reflex increase in LOS pressure (Lind, Warrian and Wankling, 1966; Cohen and Harris, 1971). In addition, previous studies of the effect of placebos on the LOS over a 30-min period revealed that no significant changes occur in barrier pressure (Cotton, Smith and Fell, 1981).

The purpose of this communication is to draw attention to the fact that the use of i.v. $\beta$-blocking drugs in clinical anaesthetic doses is likely to cause an increase in barrier pressure (and thereby confirm in humans an action similar to that in other species) and also to provoke speculation on the type of β-receptors existing at the lower end of the human oesophagus.

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### REFERENCES

Cohen, S., and Harris, L. D. (1971). Does hiatus hernia affect sphincter competence of the gastroesophageal sphincter? *N. Engl. J. Med.*, 284, 1053.

Coleman, A. J., and Jordan, D. (1980). Cardiovascular responses to anaesthesia. Influence of β-adrenoreceptor blockade with metoprolol. *Anaesthesia*, 35, 972.

Cotton, B. R., Smith, G., and Fell, D. (1981). Effect of oral diazepam on lower oesophageal sphincter pressure. *Br. J. Anaesth.*, 53, 1147.

DiMarino, A. J., and Cohen, S. (1975). The adrenergic control of lower esophageal sphincter function response to Beta$_2$ adrenergic agonists. *Proc. Soc. Exp. Biol. Med.*, 148, 1265.

Lind, J. F., Warrian, W. G., and Wankling, W. J. (1966). Responses of the gastroesophageal junctional zone to increases in abdominal pressure. *Can. J. Surg.*, 9, 32.

Rollason, W. N., and Russell, J. G. (1980). Intravenous metoprolol and cardiac dysrhythmias. An evaluation in the management of dysrhythmias in outpatient dental anaesthesia. *Anaesthesia*, 35, 783.

Weiner, N. (1980). Drugs that inhibit adrenergic nerves and block adrenergic receptors; in *The Pharmacological Basis of Therapeutics*, 6th edn, (eds L. S. Goodman and A. Gilman), p. 190. New York: Macmillan.

Whitehead, M. H., Whitmarsh, V. B., and Horton, J. N. (1980). Metoprolol in anaesthesia for oral surgery. *Anaesthesia*, 35, 779.

## PORTABLE VENTILATORS

Sir,—In our clinic we use, when necessary, a ventilator during transport of critically ill and post-operative patients. When our portable ventilators (Oxylog, Dräger and carryvent, AMI) are used, patients exhale through a non-return valve. In that situation the expiration pressure is not measured by the manometer of those ventilators. We have tested different non-return valves for this purpose. We think the Laerdal non-return valve is very suitable because it closes at low flow and the expiration resistance is low.

Recently the Laerdal company has introduced an expiration diverter to which volume meter, scavenging system or PEEP valve may be connected. In measuring the positive and expiratory pressure created by this system, we find a decreasing pressure because the expiration diverter does not fit airtight to the non-return valve.

The manufacturer states that "we have been assured by several specialists that the small leakage at this level of (10 cm) PEEP does not in a significant way reduce the desired effect".

I do not agree with them. We measured a leak of 100–150 ml$^{-1}$. With PEEP of 10 cm $H_2O$ when PEEP 15 cm was applied, the leak was 250 ml s$^{-1}$ and when PEEP 10 cm was used, 350 ml$^{-1}$. At a frequency of 15 b.p.m. and I:E ratio of 1:3 (normal for resuscitation bags) the expiration lasts 3 s. A considerable decrease in pressure may occur. PEEP pressures of 3 cm $H_2O$ are sometimes measured while PEEP 20 cm $H_2O$ is intended.

Until the manufacturer improves the design of the valve, this expiration diverter should not be used unmodified to apply PEEP to critically ill patients.

M. P. BOIDIN
*Groningen, Holland*

Sir,—We very much appreciate your concern about the leakage which may occur when using our present expiratory gas converter connected to an external PEEP device at high peak pressures. As a result of this, we have developed a modified gas converter, and we hope to be able to send you a production sample of this within a few weeks.

TORE LAERDAL
*Stavanger, Norway*

## INVOLUNTARY MUSCLE MOVEMENT

Sir,—I was interested in the observation by Klausen and his associates (1982) on the inability of buprenorphine to prevent the myoclonia associated with etomidate.

Fentanyl in doses of the order of 0.1 mg i.v. also fails to abolish etomidate-induced myoclonia. In contrast, fentanyl completely abolishes the involuntary muscle movements associated with methohexitone, so that a combination of fentanyl and intermittent methohexitone can provide satisfactory anaesthesia for short procedures (Goroszeniuk, Whitwam and Morgan, 1977). This is not true for etomidate.

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### REFERENCES

Goroszeniuk, T., Whitwam, J. G., and Morgan, M. (1977). Use of methohexitone, fentanyl and nitrous oxide for short surgical procedures. *Anaesthesia*, 32, 209.

Klausen, N.-O., Johansen, S. H., Janstrup, F., and Hansen, J. G. (1982). Preoperative buprenorphine does not prevent myoclonia seen after etomidate. *Br. J. Anaesth.*, 54, 475.

## PLATELET FUNCTION IN MALIGNANT HYPERPYREXIA

Sir,—The observation that platelet aggregation may be abnormal in patients who are susceptible to malignant hyperpyrexia (MH) (Zsigmond, Penner and Kothay, 1977), has prompted us to examine platelet aggregation as a possible predictive test to assess susceptibility to MH.

Platelet aggregation was studied in 19 individuals who were susceptible to MH and in 13 controls. In each individual, susceptibility to MH had been assessed by *in vitro* muscle contracture responses to halothane, caffeine and potassium chloride. The controls all gave normal responses to this test. Irreversible aggregation to ADP 2.5 $\mu$mol litre$^{-1}$ final concentration, adrenaline 1 $\mu$mol litre$^{-1}$, collagen 0.25 $\mu$g ml$^{-1}$, arachidonic acid 0.6 mmol litre$^{-1}$, the calcium ionophore A23187 20 $\mu$g ml$^{-1}$ and thrombin 0.1 units ml$^{-1}$ occurred in all the controls, and in all except one of the individuals who were susceptible to MH. In that one susceptible individual up to 10 times the final concentrations of ADP, adrenaline and collagen which normally give irreversible aggregation failed to produce irreversible aggregation of his platelets on three separate occasions. Aggregation in response to A23187, arachidonic acid and thrombin was always normal. The pattern of aggregation suggested a defect in the platelet release reaction, which was confirmed by studying the uptake and release of tritiated serotonin. These results are similar to those of Rosenberg and colleagues (1981), who studied platelet aggregation in five individuals who were susceptible to MH. In one of these there was a defect in the platelet release reaction, but in the other four, platelet aggregation was normal.

These results show that tests of platelet aggregation cannot be used to assess susceptibility to MH.

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REFERENCES

Rosenburg, H., Fisher, C. A., Reed, S. B., and Addonizio, V. P. (1981). Platelet aggregation in patients susceptible to malignant hyperthermia. *Anesthesiology*, 55, 621.

Zsigmund, E. K., Penner, J., and Kothay, A. P. (1977). Normal erythrocyte fragility and abnormal platelet aggregation in MH families: a pilot study; in *Second International Symposium on Malignant Hyperthermia* (ed. J. A. Aldrete and B. A. Britt), p. 213. New York: Grune and Stratton.

## ALLERGIC REACTION TO AN AMIDE LOCAL ANAESTHETIC

Sir,—The correspondence from Dr McLeskey (1981), stating in essence that allergy to amide local anaesthetics is virtually unknown, is misleading. In support of Drs Brown, Beamish and Wildsmith (1981) I would like to point out that true allergic reactions to amide local anaesthetic drugs are by no means unknown to dentists, who administer them to many more patients than we do.

Noble and Pierce (1961), Waldman and Binkley (1967), Eyre and Nally (1971) and Walker (1971) all reported cases of true allergy to lignocaine, while Halpern, Ky and Amache (1967) cited four patients in whom lignocaine hypersensitivity was authenticated by lymphocyte transformation test. Reference to some of these may be found in a standard textbook of anaesthesia (Reynolds, 1978).

Felicity Renolds
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REFERENCES

Brown, D. T., Beamish, D., and Wildsmith, J. A. W. (1981). Allergic reaction to an amide local anaesthetic. *Br. J. Anaesth.*, 53, 435.

Eyre, J., and Nally, F. F. (1971). Nasal test for hypersensitivity including a positive reaction to lignocaine. *Lancet*, 2, 264.

Halpern, B., Ky, N. T., and Amache, N. (1967). Diagnosis of drug allergy *in vitro* with the lymphocyte transformation test. *J. Allergy*, 40, 168.

McLeskey, C. H. (1981). Allergic reaction to an amide local anaesthetic. *Br. J. Anaesth.*, 53, 1105.

Noble, D. S. and Pierce, G. F. M. (1961). Allergy to lignocaine; a case history. *Lancet*, ii, 1036.

Reynolds, F. (1978). The pharmacology of local anaesthetic drugs; in *A Practice of Anaesthesia* (ed. H. C. Churchill-Davidson), p. 1105. London: Lloyd Luke.

Waldman, H. B. and Binkley, G. (1967). Lignocaine hypersensitivity; a report of a case. *J. Am. Dental Assoc.*, 74, 747.

Walker, R. T. (1971). Hypersensitivity reaction to local anaesthetic (letter). *Brit. Dent. J.*, 130, 2.

# BOOK REVIEWS

*Cardiac Anaesthesia.* Edited by Thomas J. Conahan III. Published by Addison–Wesley Publishing Co. Inc. Pp. 340; illustrated; indexed. Price $29.95.

In the preface, the editor states that the goal is to provide an overview of the problems that bring patients to cardiac surgery and the surgical procedures performed to alleviate those problems. The text is clearly and concisely laid out, each chapter following clearly a format which starts with a notation of its contents and essential pages, and finishes with an excellent up to date list of references to aid with further reading.

In addition to techniques of diagnosis, natural history and surgical approach to congenital and acquired heart disease—all of which are written in an easily comprehensible style—there are interesting and informative chapters on perfusion techniques, myocardial preservation, monitoring and postoperative intensive care.

Pharmacological adjuvants and haemostatic mechanisms are also well covered, although the British reader must be aware of American drug terminology. This also applies to the actual anaesthetic techniques discussed; these, as recorded, are American techniques which differ in many aspects from conventional British practice.

Diagrams, charts, illustrations and classifications are good, but it is regrettable that heparin dose is recorded by one author in milligrams instead of international units.

This book achieves the editor's goal and rightly deserves a place on many people's bookshelves. The authors and the editor have given us an informative "basic text for the resident and the practitioner".

*Jean Lumley*

*Anesthesia and the Obese Patient.* Edited by Burnell R. Brown jr. Published (1982) by F. A. Davis Company, Philadelphia. Pp. 139; illustrated; indexed. Price $27.50.

Severely overweight patients pose practical difficulties for the anaesthetist and surgeon. Obesity is mainly a problem in Western countries, especially the U.S.A. As this book says several times, the U.S. "norm" for body fat is changing as obesity there becomes more usual.

This slim volume has been written mainly by Professor Robert Vaughan of the University of Arizona Health Sciences Center in Tucson. He has anaesthetized hundreds of patients for operations to reduce obesity and has studied aspects of their management, mainly arterial oxygenation, but also enflurane metabolism, gastric juice and anaesthetic techniques. The book's stated intention is to be "pragmatic and informative, but certainly not comprehensive", but it becomes clear that it is mainly about elective abdominal surgery in such patients. A topic of considerable current interest that is not mentioned in the book is the occurrence of respiratory disturbances in obese subjects during sleep, leading to hypoxia and possibly pulmonary hypertension and cardiac arrhythmias.

Information about disturbed respiratory, circulatory and hepatic physiology, and the medical consequences of severe obesity, is sparse. Four of the chapters review this information, but without a great deal of criticism or conclusion. The exceptions are the accounts of the liver in obesity and the relationship between obesity, decreased lung volume and closing capacity, which is used to explain arterial hypoxaemia in these patients. Unfortunately, the practical implications of this phenomenon, particularly recommendations for the treatment of postoperative hypoxaemia, are not clearly made.

The cardiovascular effects of excess body fat are less clearly explained. Extra fat must need extra blood and blood flow, and excess weight correlates with an increase in these variables. However, it is not clear how much extra flow is needed by this extra tissue, which is not metabolically highly active, and how much is needed by the heart and muscle that have to support it.

In his review of the metabolism of anaesthetic agents, Professor Vaughan chooses to ignore work done in the United Kingdom on liver enzyme changes after inhalation anaesthesia and bromide formation after halothane anaesthesia. The occassional slip suggests that the author's forte is in clinical matters. Maximum mid-expiratory flow, for example, as measured by the author in one of his studies, is *not* the same as peak expiratory flow rate. One would hope for more from the clinical section of the book, but the advice is general. For instance, advice that "with awareness of the effects of volatile anaesthetics in obese subjects, an informed consultant in anaesthesia can make a prudent decision for management of each individual obese patient" would meet with a predictable response if it were read by an examiner marking a Fellowship essay question! Advice on the nursing care of very fat patients offers some fascinating practical advice on transport and handling problems, but again the reader is left searching for a practical message, for example, after an erudite description of how fat patients differ little from normal subjects in having a reduced core temperature after surgery. Is this not mainly because of the more even distribution of body heat during anaesthesia? The core temperature seems to return to normal without treatment; at least no treatment is proposed!

The book is not inexpensive, but it is well produced with hardly any printing errors. The editor comments that the derangements produced by the obese state are ponderous: so too are his comments! This book would be a useful addition to a large departmental library, but does not contain a great deal of practical guidance. Perhaps if intragastric balloons or pieces of string become accepted techniques in reducing the dietary intake of fat patients, elective abdominal surgery in the grossly fat may become of historical interest!

*GordonDrummond*

*Inherited Disease and Anaesthesia, 1981. Monographs in Anaesthesiology, 9.* Edited by F. R. Ellis. Published by Elsevier/North-Holland Biomedical Press, Amsterdam. Pp. 463; illustrated; indexed. Price $105.00.

Dr Ellis is to be congratulated on putting together this multi-author monograph. In a book of 436 pages he has succeeded in achieving an admirable balance between a text which is easy to read and yet large enough to act as a source of reference. It provides a comprehensive review of inherited medical conditions which may be important to a clinical anaesthetist. It is not a source of the details of clinical management, but it does indicate where relevant the implications and the "do's and dont's" of the problem. The general chapters at the beginning, on medical genetics, and at the end on probability and inherited disease, provide the reader with a relatively painless entry into these difficult subjects and are sufficiently well referenced to act as a starting point for anyone wishing to take the subject further.

The chapter on tissue typing and organ transplantation does not fit easily into this book, since the rest of it concerns the genetically abnormal whereas tissue typing is concerned with the best fit of normal tissues and avoiding incompatibility of otherwise normal immune systems. Unlike the rest of the book, where the inherited abnormality may be of vital concern in anaesthetic management, in organ transplantation the anaesthetic problems are technical and the details of tissue typing are hardly the province of the anaesthetist. More relevant would be a discussion of abnormal immunology as it affects the anaesthetist, and this is a separate subject. In the section on malignant hyperpyrexia, owing to the selective nature of the bibliography (18 out of 68 refer to Dr Ellis' own work) there are important omissions, for example to the work of Gronert from the Mayo Clinic on the pathophysiology of the syndrome.

It is surprising to see a chapter on Familial Stress Syndrome in a text book as if this syndrome were a clearly defined and accepted entity. This is still a controversial area and perhaps it would have been better discussed as such in the previous chapter on Malignant Hyperpyrexia. In the section on sickle disease there is no reference to the important problem which may face an anaesthetist on emergency duty of defining potentially dangerous patients—those with SC disease—as distinct from those who are relatively "safe"—SA, who have normal haemocrits when electrophoresis for haemoglobin analysis may not be immediately available.

Nonetheless, subject to these minor criticisms, this is a book which any department could usefully add to its library.

*J. G. Whitwam*

*Anaesthesia and Recovery Room Techniques*, 3rd edition. By Jennifer Wachstein and Jean A. H. Smith. Published (1981) by Baillière Tindall. Pp.165, illustrated; indexed. Price £4.75.

The latest edition of this popular textbook in the Nurses Aid Series has been expanded to make it suitable for inclusion in the Special Interest Texts. It is designed to meet needs of nurses in general training and of those undergoing post-basic training. The book has been enlarged mainly by the addition of a chapter on "Hazards to Theatre Staff" which examines the implications of the Health and Safety at Work Act (1974) to the nurse in theatre, under such headings as radiation, lasers, cross-infection, serum hepatitis, polution and stress. It has been further enlarged by the expansion of the sections on basic physiology and pharmacology and by the inclusion of essay and MCQ-type questions.

The early chapters on the preparation of the patient for theatre, both physically and psychologically, the preparation of the anaesthetic room and the care of the anaesthetized patient are excellent and could be usefully read by all grades of theatre staff; they remain largely unchanged from the second edition. I gratefully acknowledge the helpful comments of Sister Susan Beale S.R.N. on these opening chapters.

Some of the illustrations are inaccurate; figure 2, which shows Sellick's manoeuvre, does not label any of the relevant structures and shows pressure being applied over the trachea. Diagrams such as figure 4 which illustrates Moynihan's tongue forceps could well have been omitted and figure 31, depicting Schimmelbusch mask with accompanying text suggesting that the nurse may see it used with ethyl chloride "in an emergency", is surely inappropriate. A grossly abnormal electrocardiogram in figure 52 is labelled as "a normal trace".

I have grave doubts about the expanded sections of physiology and pharmacology, much of it is muddled (e.g. the physiology of neuromuscular transmission p. 99), and some totally wrong. The statement is made (p. 100) that non-depolarizing relaxants block the action of acetylcholine on the motor end-plate and prevent normal depolarization from taking place; it is concluded that "This is an anticholinesterase action: these drugs permit the build-up acetylcholine". The pharmacology is also suspect; "Drugs given to lower blood pressure are known as ganglion blocking agents" and the list given in illustration of this statement includes mecamylamine (unavailable in parenteral form in this country) and sodium nitropurssside. It was pointed out in a review of the previous edition that lignocaine did not "improve cardiac tone"; this error has gone uncorrected, and the information that the "maximum safe dose (of lignocaine) is 350 mg plain" is frankly dangerous. There are many other errors of fact, and didactic attitudes are adopted which would be inappropriate in other centres; I would not, for example, wish a theatre nurse to hook her little finger in the patient's mouth during every intubation.

It is a great pity that in "extending the scope" of this useful little book errors have been allowed to creep in which often render it, at best, misleading. The early appearance of a fourth edition is to be encouraged with a more thorough re-write and the inclusion only of that which is relevant.

*David Saunders*

*Anaesthesia and Uncommon Diseases. Pathophysiologic and Clinical Correlations.* By J. Katz, J. Benumof and L. Kadis. Published (1981) by W. B. Saunders. Pp. 807; illustrated; indexed. Price £34.75.

How often one is asked, or asks oneself, if a particular condition, particularly one not met before, introduces any additional but avoidable anaesthetic hazards. This book may provide the answers to such a question. By way of introduction there is a rather forbidding chapter "Inborn Errors of Metabolism". Some of this is hard going but, on the other hand, if you wish to know about the anaesthetic problems presented by a patient with Transferase Deficiency Galactosaemia, this might be the book to give you the answer.

Each chapter begins with a well written and detailed account of the influence of the disease on normal function, followed by the implications for anaesthesia.

The genetic and biochemical derangements which underly the hepatic porphyrias are clearly explained, but apart from indicating the "relative paucity of porphyric patients", there is little to indicate my chances of meeting a patient with these fortunately rare conditions. On the other hand the frequency of phenylketonuria is described in detail, ranging from 1:40 in gipsy populations to 1:15000 in Japan. Other rare hereditary disorders are discussed including Ehlers–Danlos and Chediak–Higashi syndromes.

One has to niggle at some statements such as "only organ size and brain development may be affected" to be found in the chapter "drugs, the developing foetus and newborn". "Only" seems to be an odd value statement to associate with brain impairment.

In "Anaesthesia for the Geriatric Patient", one is introduced to the unexpected concept that age is a rare condition. While 10% of the population of the United States is over the age of 65 years, this population size diminishes exponentially so that less than 1% of the population is older than 75 years and furthermore, because only a small fraction of these undergo general anaesthesia, old age represents a relatively uncommon condition when considering general anaesthesia. I am sure the reader will recognize that, although elderly patients may only be a small fraction of the general population, they still constitute a large fraction of the hospital population, and therefore I cannot agree that old age is a rare condition when considering anaesthesia.

I should like to illustrate the range within this book, not by considering the sections on muscle diseases, connective tissue diseases, neurological disease or skin and bone disorders, but rather by special reference to a single section—gastrointestinal disorders. Like all sections this starts simply enough with a discussion of nausea and vomiting. There are the details of neurophysiological control which are followed by a consideration of acid–base impairment. The information in this book is not always confined to rare conditions. A comment on the varieties of fistula is followed by analysis of the problems associated with gastrointestinal obstruction at different sites. One finds here occasional rather teleological statements, although they may be emotionally satisfying, such as "in an attempt by the body to conserve $HCO_3$. . . ." While constipation, diarrhoea and gastrointestinal bleeding might not themselves be considered rare events they may result from uncommon diseases. However, the chapter does get into top gear with the aetiologies of malabsorption. As the reader proceeds distally down the oesophagus and beyond, syndromes tumble after one another, Boerhaaves, Barett's and Zollinger–Ellison are described, as are many others until finally we get back to vomiting.

You may not agree absolutely with everything in this book, but there is a wealth of the unexpected diseases; not very common, any of them, but beware that 2 a.m. call from the registrar.

*T. E. J. Healy*

*Obstetric Analgesia and Perinatology*. By Ermelando V. Cosmi. Published (1981) by Prentice/Nall International. Pp. 769; illustrated; indexed. Price £31.90.

This book claims to present in detail the major problems encountered in the field of obstetric analgesia and anaesthesia and is intended for anaesthetists and for others who have entered the field of perinatal medicine.

The stated plan of the book is to review the older literature, to provide new information and to suggest guidelines for future developments. Because of the current trend to "natural childbirth" both the positive and negative aspects of the use of sedatives, analgesics and anaesthetics during labour are presented.

An international team of 20 authors contribute 19 chapters of variable length. Inevitably the style of writing and ease of reading is uneven. The first six chapters deal with the psychological and physiological adaptations to pregnancy and parturition and include sections on psychoprophylaxis and hypnosis. Three chapters cover the effect of anaesthesia on uteroplacental blood flow, on labour and delivery and on the fetus. Other topics include hypertension and diabetes in pregnancy, management of preterm labour, and neonatal lung physiology and adaptation. By far the longest single contribution is the chapter on fetal homeostasis, extending to 216 pages with a vast list of 1388 references!

Anaesthetists will find that this book is not a guide to techniques and may be disappointed by the lack of information on important topics. Regional Analgesia in Obstetrics occupies only 14 pages of text with 154 references.

The book is biased towards an American readership and current American practice of obstetric anaesthesia, as indicated by the chapter on hypertension in pregnancy, much of which is an elequent argument against the use of magnesium sulphate and in favour of methods commonly used in Britain.

In a book of this nature some repetition cannot be avoided and if a topic is to be discussed from different points of view some contradiction is unpreventable, but sometimes confusing. The surprising statement, on the use of diazepam in obstetrics, that no untoward effects on the mother or newborn have been found after the administration of doses as great as 100 mg (p. 403), is fortunately challenged elsewhere in the book.

Some of the chapters are inconclusive and present arguments, ideas and propositions rather than didactic advice on practical obstetric anaesthesia and analgesia. The last two are an exception, the penultimate presenting a lucid account of the practical aspects of neonatal resuscitation.

*Melville K. Milne*

OTHER BOOKS RECEIVED

*Convergences Médicales*, Tome 1, Nos. 1 and 2, 1982. Organe officiel de l'Association "Convergences" pour la publication de travaux medicaux convergents. No. Commission Paritaire 52346. Dépôt légal; $1^{er}$ trimestre 1982. Imprimerie P. Guichard, 4, rue E. Martel – 42100 Saint-Etienne.

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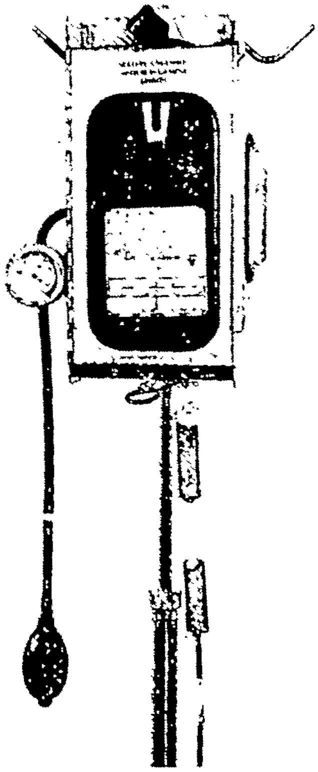

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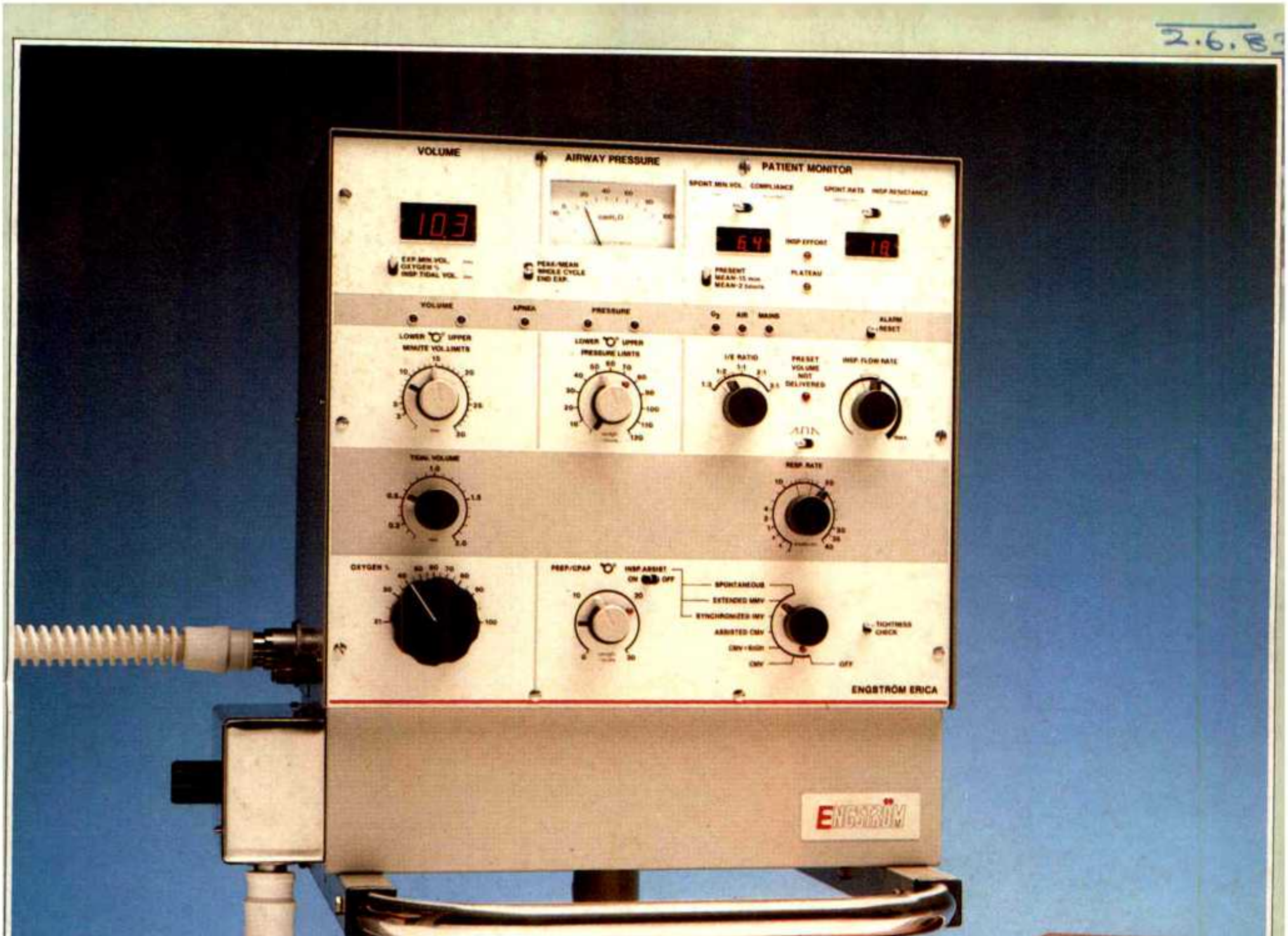

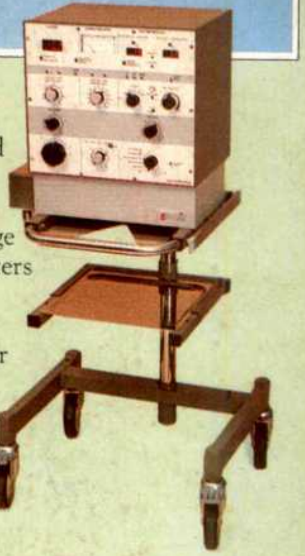

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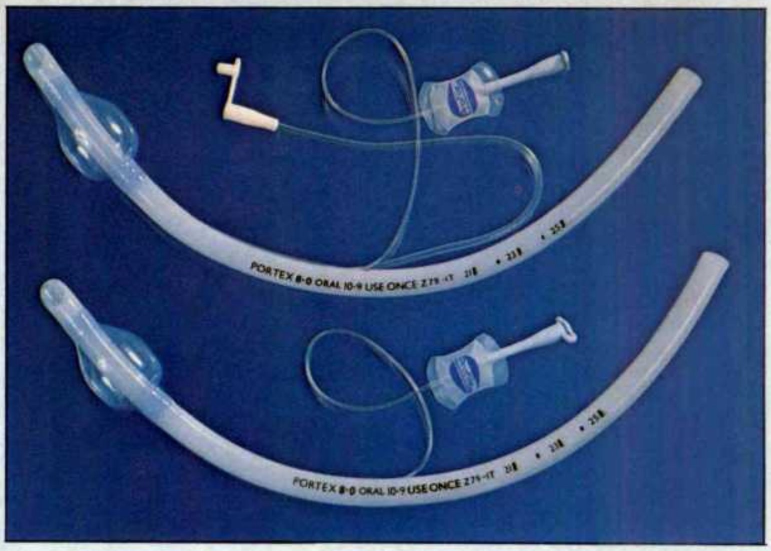

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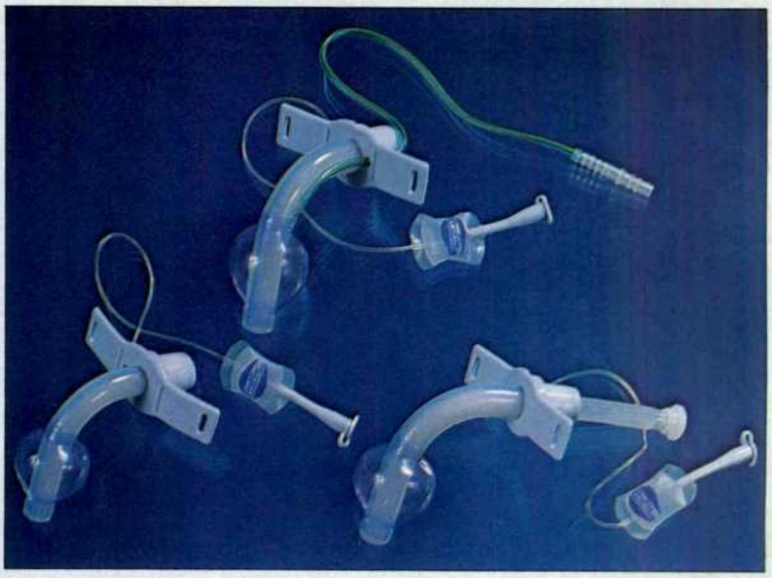

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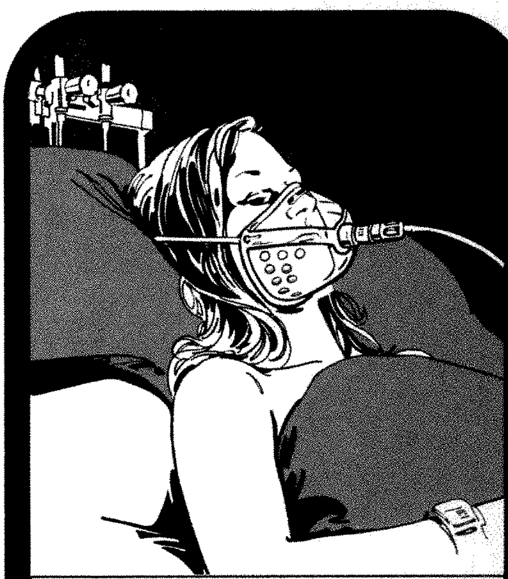

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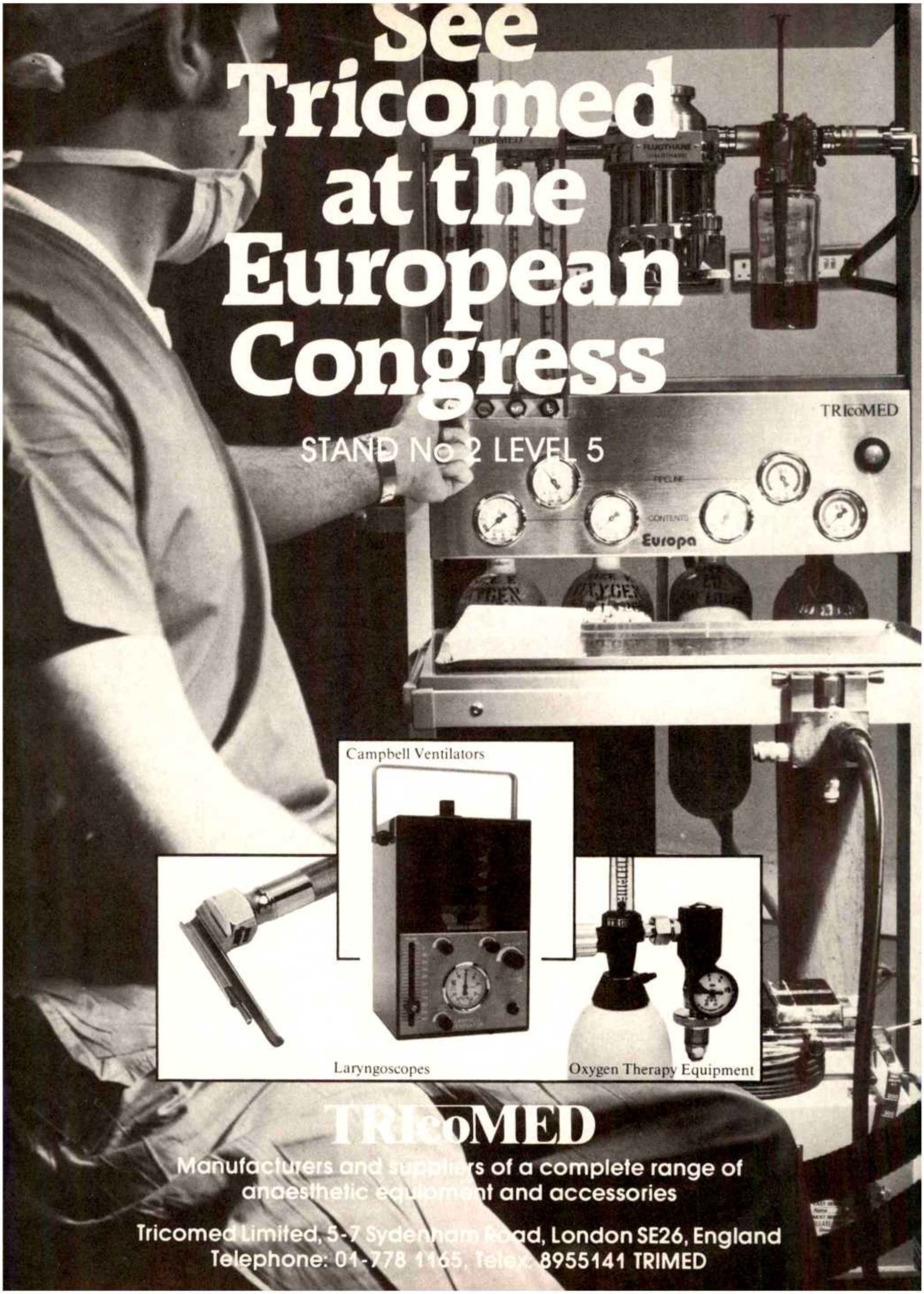

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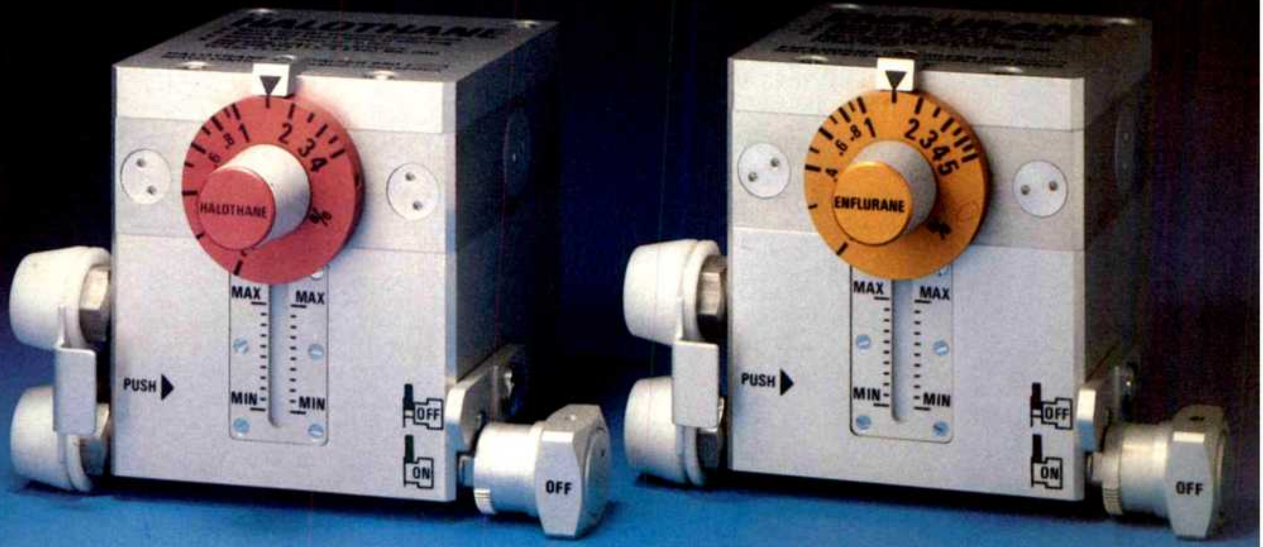

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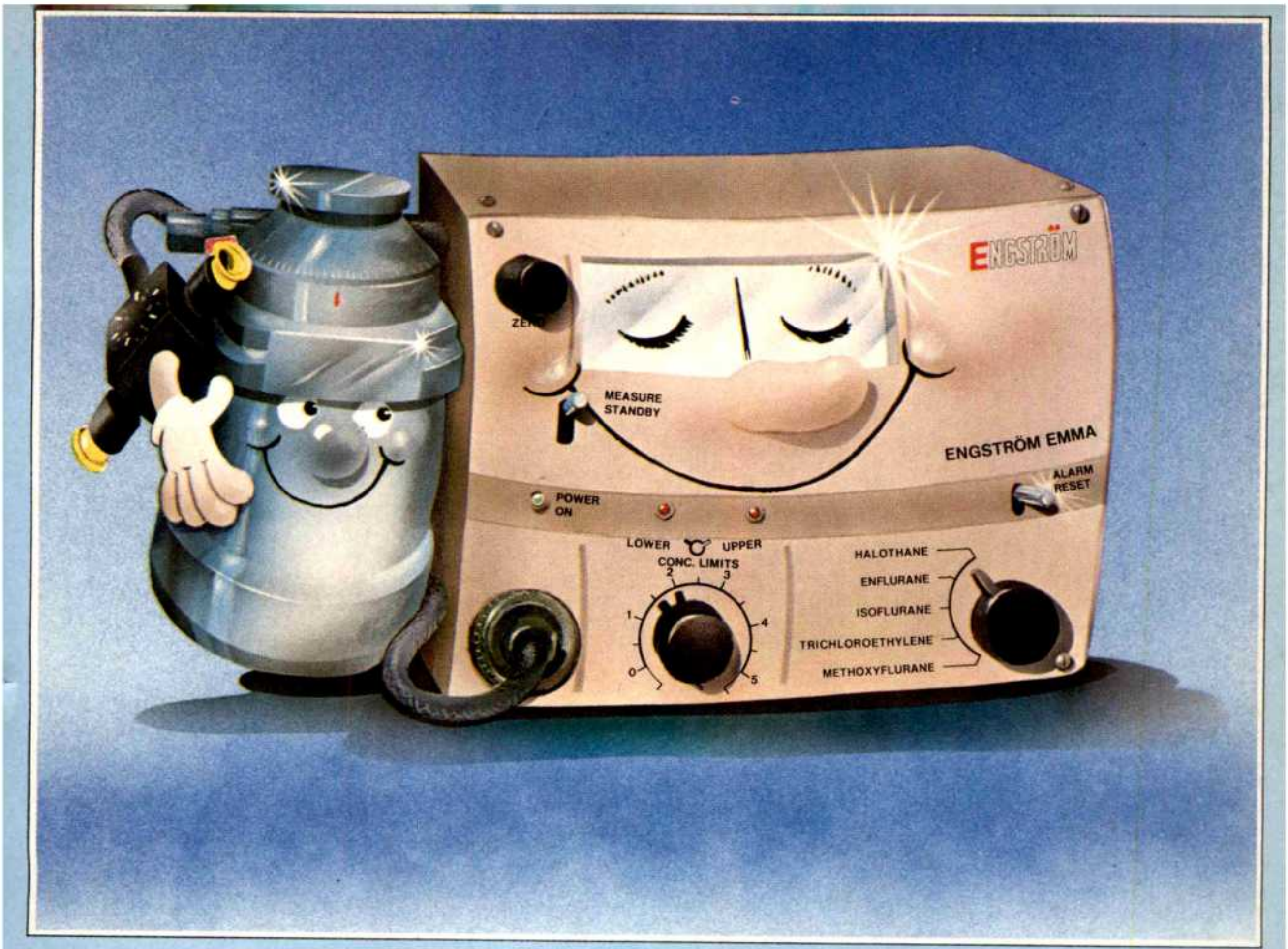

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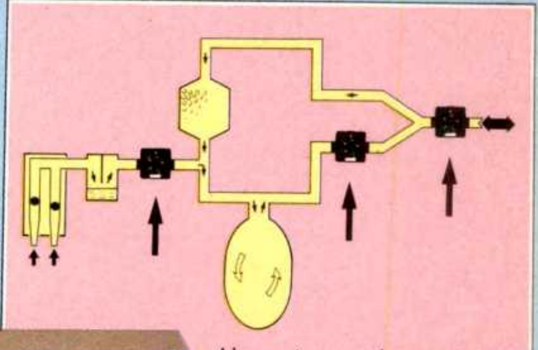

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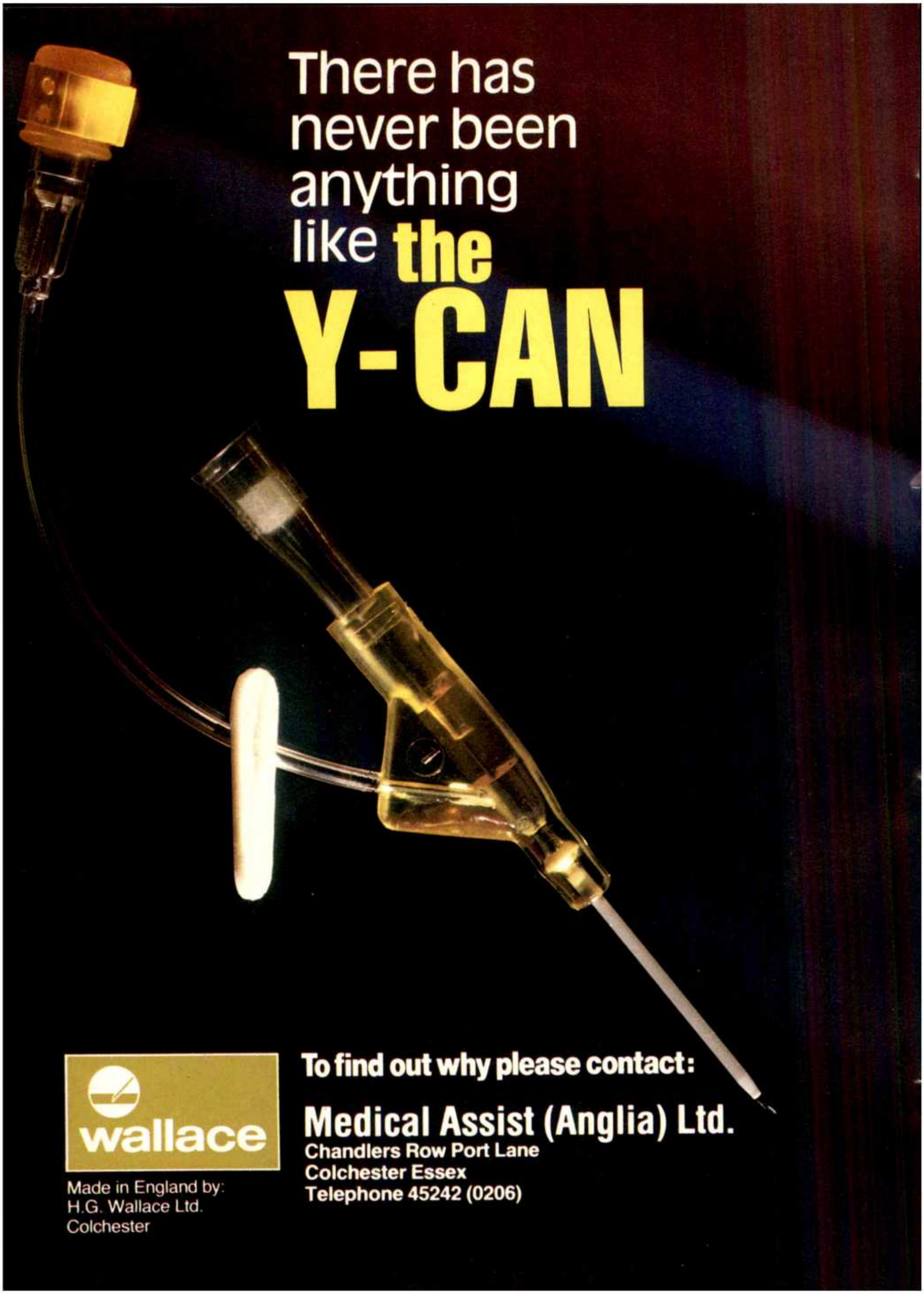

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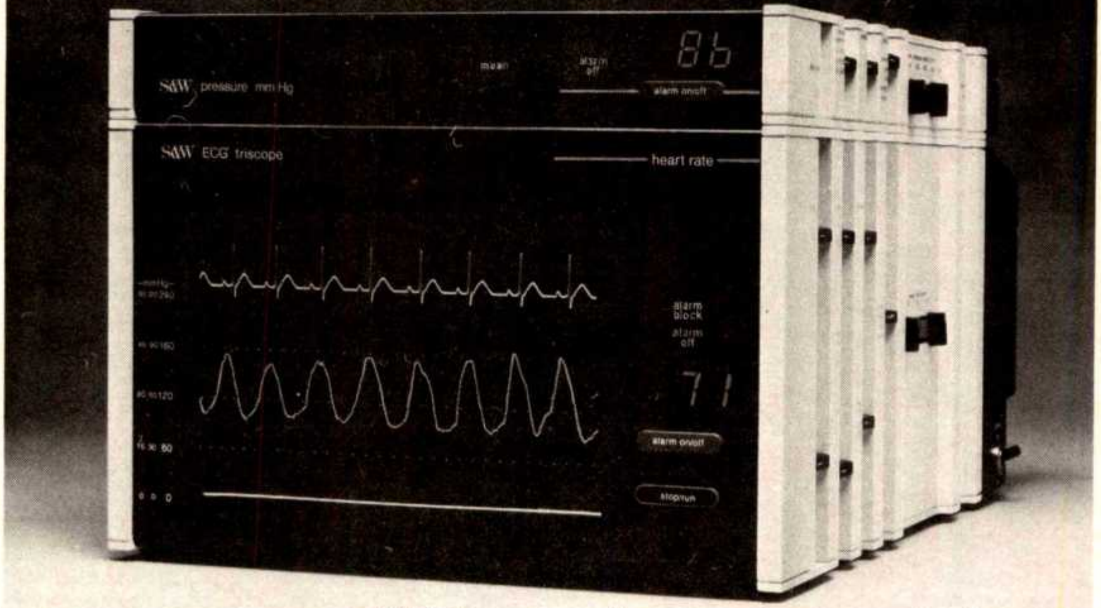

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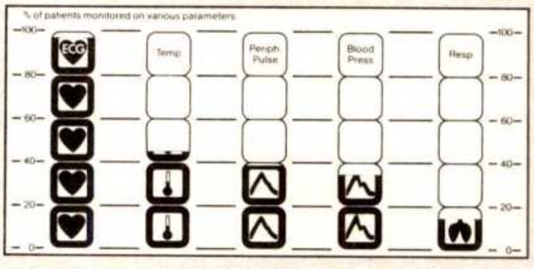

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# EDITORIAL

## BROWN FAT—A THERMOGENIC TISSUE OF ANAESTHETIC IMPORTANCE?

Heat production on exposure to cold may occur either by shivering or other processes known collectively as non-shivering thermogenesis (Himms-Hagen, 1976). The major site of non-shivering thermogenesis is brown-adipose tissue (BAT). Recent work with small rodents has shown that BAT is important during cold adaptation and that it is also capable of increasing heat production during overfeeding (diet-induced thermogenesis). Furthermore, there is evidence that in some forms of genetically determined obesity (the ob/ob mouse), weight gain is mainly a result of defective function of BAT. The relevance of these findings to man is under intensive investigation at present.

Exposure of the rat to cold is associated with an increase in size of BAT to 1–2% of total body weight (Foster and Frydman, 1978). BAT has a rich sympathetic innervation which can be activated by stimulation of the ventromedial nucleus of the hypothalamus. The effects of noradrenaline in stimulating heat production can be inhibited by β-adrenergic blocking drugs. The mitochondria in the fat cells are specially adapted for thermogenesis as they have a proton conductance pathway in the inner membrane of the mitochondria associated with a protein of 32 000 molecular weight (Nicholls, 1977). The operation of this pathway, and hence the degree of uncoupling of oxidative phosphorylation, is regulated by purine nucleotides such as guanosine diphosphate (GDP) and the supply of substrate in the form of acyl-CoA. The nucleotides inhibit the proton conductance pathway by binding to the protein on the outer surface of the inner mitochondrial membrane.

The increased metabolic expenditure induced by overeating in rats, diet-induced thermogenesis, is a result of more effective heat production in BAT (Rothwell and Stock, 1979). For example, the overfeeding of rats using a palatable diet ("cafeteria-fed") does not produce any significant increase in body weight in spite of a two-fold increase in food intake. During this period of overfeeding there is a large increase in the size of the interscapular BAT, which is a result of both hyperplasia and hypertrophy. The increase in BAT activity in "cafeteria-fed" rats is shown by an augmented response in whole body oxygen consumption to a noradrenaline infusion, which is caused largely by an increased oxygen uptake by BAT. In effect, therefore, rats can be cold-adapted by overfeeding.

An increase in the size of BAT, however, does not necessarily reflect an increase in heat production. In the genetically obese (ob/ob) mouse, which is characterized by its failure to maintain body temperature in a cold environment (Trayhurn and James, 1978), BAT is present in normal or increased amounts, but thermogenesis is defective. This failure of heat production is associated with a decrease in guanosine diphosphate (GDP) binding to the mitochondrial membrane.

In man, it is well known that BAT is an important site of thermogenesis for the neonate before the shivering mechanism becomes fully developed. The role of BAT in the adult is more controversial, but Heaton (1972) has shown that BAT persists in sites such as the interscapular, perirenal and inguinal regions, and in the posterior triangle of the neck. However, the morphological distinction between brown and white adipose tissue is less obvious in adult man than in small rodents. Rothwell and Stock

(1979) observed that the administration of oral ephedrine was associated with an increase in heat radiation from the skin over sites at which BAT is thought to be present in the adult.

Non-shivering thermogenesis in man is most easily demonstrated by exposure to cold (Joy 1963). Huttunen, Hirronen and Kinnula (1981) showed recently that there was a large increase in BAT in Scandinavians who worked outside during the winter. Andrews and Jackson (1978) found a difference in heat production between obese and lean individuals on exposure to cold. Whereas some of the former had a decrease in core temperature, all the lean subjects maintained their body temperature. These results suggest that obesity, perhaps secondary to impaired thermogenesis in BAT, may be associated with failure of heat production in a cold environment. Jessen (1980) showed the occurrence of non-shivering thermogenesis in paralysed patients in an intensive care unit. A decrease in core temperature of 0.8 °C was associated with a 40% increase in whole body oxygen consumption, a three-fold increase in circulating noradrenaline and marked stimulation of lipolysis. It was not possible to determine whether the increase in heat production was derived from brown or white adipose tissue.

Diet-induced thermogenesis in man was first noted by Neumann (1902) who used the term luxusconsumption to describe the production of extra heat as a response to increased food intake. Sims (1976) found that several months of overfeeding with an increase in energy intake from 12.6 to 23.8 $\mathrm{mJ\,day^{-1}}$ produced only a slight increase in body weight. There is, at present, only a little indirect evidence to support the contention that some forms of obesity in man are caused by a thermogenic defect in BAT. Jung and colleagues (1979) found a similar decrease in the thermogenic response to noradrenaline in obese subjects compared with lean subjects to that observed by Trayhurn and James (1978) in the genetically obese mouse.

Although the work described above is of great physiological, and possibly clinical, significance, any application to anaesthetic practice may not be immediately apparent. Indeed, the knowledge that a grossly obese patient has defective thermogenesis in the mitochondria of the BAT is interesting, but of no value in managing the anaesthetic problems associated with obesity. However, heat production by BAT may be involved in several physiological responses found during and after surgery. For example, the exposure of an anaesthetized, paralysed patient to a cold environment will induce non-shivering thermogenesis which should be greater in lean than obese subjects. Since activation of BAT inevitably induces an increase in oxygen consumption, any difference in the thermogenic response is important.

It is important for the practice of anaesthesia that all possible factors responsible for heat balance during the operative and post-operative period are fully elucidated. Further studies of BAT are necessary before it can be determined if this thermogenic tissue is significant but the pursuit of these seems highly relevant.

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REFERENCES

Andrews, F., and Jackson, F. (1978). Increasing fatness inversely related to increase in metabolic rate but directly related to decrease in deep body temperature during cold exposure. *Irish J. Med. Sci.*, **147**, 329.

Foster, D. O., and Frydman, M. L. (1978). Non-shivering thermogenesis in the rat II. Measurements of blood flow with microspheres point to brown adipose tissue as the dominant site of calorigenesis induced by noradrenaline. *Can. J. Physiol. Pharmacol.*, **56**, 110.

Heaton, J. M. (1972). The distribution of brown adipose tissue in the human. *J. Anat.*, **112**, 35.

Himms-Hagen, J. (1976). Cellular thermogenesis; in *Annual Review of Physiology* (eds E. Knobil, R. R. Sonnenschein and I. S. Edelman), p. 315. California, USA: Annual Reviews Inc.

Huttunen, P., Hirronen, J., and Kinnula, M. (1981). The occurrence of brown adipose tissue in outdoor workers. *Eur. J. Appl. Physiol.*, **46**, 339.

Jessen, L. (1980). An assessment of human regulatory non-shivering thermogenesis. *Acta Anaesthesiol. Scand.*, **24**, 138.

Joy, R. J. T. (1963). Responses of cold-acclimatized men to infused norepinephrine. *J. Appl. Physiol.*, **18**, 1209.

Jung, R. T., Shetty, P. S., James, W. P. T., Barrand, M. A., and Callingham, B. A. (1979). Reduced thermogenesis in obesity. *Nature (Lond.)*, **279**, 322.

Neumann, R. O. (1902). Experimentalle Beigrage zur Lehre von dem täglichen Nahrungsbedarf des Menschen unter besonderer Berucksichtigung der notwendigen Eiweissmenge. *Arch. Hygiene.*, **45**, 1.

Nicholls, D. G. (1977). Brown adipose tissue mitochondria. *Biochem. Biophys. Acta*, **549**, 1.

Rothwell, N. J., and Stock, M. J. (1979). A role for brown adipose tissue in diet-induced thermogenesis. *Nature (Lond.)*, **281**, 35.

Sims, E. A. H. (1976). Experimental obesity, dietary-induced thermogenesis and their clinical implications. *Clin. Endocrinol. Metab.*, **5**, 277.

Trayhurn, P., and James, W. P. T. (1978). Thermoregulation and non-shivering thermogenesis in the genetically obese (ob/ob) mouse. *Pfluegers Arch.*, **373**, 189.

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# ATRACURIUM: ITS SPEED OF ONSET. A COMPARISON WITH SUXAMETHONIUM

R. P. F. SCOTT AND V. A. GOAT

## SUMMARY

Forty healthy patients were randomly selected to receive either atracurium 0.6 mg kg$^{-1}$, or suxamethonium 1 mg kg$^{-1}$. Onset of neuromuscular blockade and the time to full peripheral paralysis were measured using a train-of-four stimulus repeated once every 12 s. Atracurium appeared to be a potent non-depolarizing muscle relaxant, with a rapid onset of action. However, full peripheral paralysis took longer to achieve than with suxamethonium. There were no significant problems with recovery.

Atracurium dibesylate is reported to be a potent non-depolarizing muscle relaxant in both laboratory animals (Hughes and Chapple, 1980; Hughes and Chapple, 1981) and man (Hunt, Hughes and Payne, 1980). It is a short-acting agent and a qualitative evaluation of the drug has suggested that it has a rapid onset of action (Payne and Hughes, 1981).

There have been many studies to evaluate the speed of action of muscle relaxants. In some, judgement of paralysis has been largely subjective, using clinical criteria such as jaw relaxation, ease of tracheal intubation and the absence of response to laryngoscopy and intubation (Harrison and Feldman, 1981; Hey, 1973). Despite all efforts to eliminate bias, ease of intubation will depend not only upon the degree of neuromuscular blockade, but also upon the depth of anaesthesia, the anatomical configuration of the patient and not least upon the skill of the anaesthetist. An objective comparison of the rate of onset of neuromuscular blocking drugs can best be obtained by recording the response of a muscle to stimulation of its motor nerve.

In this study the speed of action of atracurium was monitored using a repeated 2-Hz train-of-four stimulus, and compared with suxamethonium. This comparison was chosen since the fast onset time reported in a preliminary study (Payne and Hughes, 1981) had suggested to the investigators that this new non-depolarizing muscle relaxant could well be used as an alternative to suxamethonium.

## METHOD

Forty healthy patients undergoing minor dental surgery requiring intubation were studied. The patients, who gave informed consent to the trial, were between 18 and 45 years of age. Any patient receiving concurrent medication, apart from the contraceptive pill, or in whom pregnancy was suspected, was excluded. Ethical consent for this study was obtained and the trial was conducted with the authority of a clinical trial certificate issued by the Committee on the Safety of Drugs.

After premedication with papaveretum and hyoscine, a modified Elcomatic transducer (Armstrong, Goat and Loach, 1977) was attached to the patient's dominant hand and positioned to achieve maximal mechanical response to thumb adduction. Anaesthesia was induced with fentanyl 3 $\mu$g kg$^{-1}$ and thiopentone 5 mg kg$^{-1}$, and maintained with nitrous oxide and oxygen; ventilation of the lungs was assisted via a face-mask. Stimulation of the ulnar nerve at the wrist was carried out via cutaneous electrodes, using a Grass S48 nerve stimulator and S1U5 isolation unit. The stimulus width was 0.2 ms. Once it was certain that the stimulus was supramaximal, the stimulator was set to produce a 2-Hz train-of-four stimulus, repeated once every 12 s. The mechanical response to nerve stimulation was measured by the transducer and displayed on an Elcomatic recorder.

The patients had been randomly selected to receive either atracurium 0.6 mg kg$^{-1}$ of suxamethonium 1 mg kg$^{-1}$, diluted to the same volume for injection. All drugs were administered via a peripheral indwelling needle, and the relaxant injected at the time of nerve stimulation, the start of

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injection coinciding with the first stimulus of the train. The time from the administration of the muscle relaxant to the first depression of any response in the train was noted. This was called the onset time. The time at which full peripheral paralysis occurred was also noted. At this time no recorded response was obtained from the stimulus. Tracheal intubation was attempted by one of the authors (V.A.G.) at full peripheral paralysis, using the nasal route under direct vision.

During induction of anaesthesia, the e.c.g. was monitored continuously to detect changes in heart rate. After intubation 1% halothane was added to the anaesthetic; this concentration was reduced during surgery to allow a rapid return of consciousness at the end of the procedure. Neuromuscular monitoring was not continued during surgery, and at the completion of the operation, those patients who had received atracurium were given neostigmine 2.5 mg with atropine 1.2 mg. The time of administration of these drugs was noted, and reversal of paralysis shown by the ability of the patient to maintain a head-lift for 5 s (Dam and Guldmann, 1961).

After operation all patients received standard analgesic and antiemetic drugs and were interviewed at 24 h. They also received a questionnaire which they were asked to return after 72 h, in order to detect any major problems.

Results were analysed using the unpaired two-tailed Student *t* test.

## RESULTS

The results are summarized in table I. Patients were evenly distributed according to age and weight in both groups. The onset of neuromuscular block was faster by almost 15 s in those patients receiving suxamethonium, and this difference in onset time is significant.

Full peripheral paralysis occurred in all patients in both groups. A highly significant difference was seen in the time to full peripheral paralysis, with atracurium taking nearly twice as long as suxamethonium.

Retrospective analysis of the data showed that in several cases in both groups full peripheral paralysis had been anticipated, and intubation had commenced on the penultimate train-of-four. This gave an inconsistent starting point for intubation and intubating conditions between the drugs could not be compared reliably.

Changes in heart rate were minimal in both groups and there was no significant difference between the two groups (table II). No specific problems were encountered after operation in those patients receiving atracurium, although 11 patients in the suxamethonium group complained of moderate to severe muscle pains.

TABLE II. *Heart rate change*

| | No. patients | No. with heart rate change | |
|---|---|---|---|
| | | $>10$ beat min$^{-1}$ | $<10$ beat min$^{-1}$ |
| Suxamethonium | 20 | 2 | 2 |
| Atracurium | 20 | 2 | 2 |

## DISCUSSION

The speed of onset of atracurium has been studied by others (Payne and Hughes, 1981), who followed the time course of blockade by using the response of the adductor pollicis muscle to repeated tetanic stimulation. The mean onset of maximal effect was reported to be 1.2 min at a dose of 0.6 mg kg$^{-1}$. The time to full peripheral paralysis in this study was just over 2 min (129 s). The discrepancy between these

TABLE I. *Patient characteristics and neuromuscular blockade data. Significance (Student's* t *test): *P <0.01, **P <0.001*

| | No. of patients | Mean age (yr) | Mean wt (kg) | Male | Mean time to onset of paralysis (s) | Mean time to full peripheral paralysis (s) |
|---|---|---|---|---|---|---|
| Suxamethonium | 20 | 24.9<br>(SD 5.4) | 64.9<br>(SD 11.9) | 10 | 34.8<br>(SD 11.6) | 69.9<br>(SD 18.5) |
| Atracurium | 20 | 24.3<br>(SD 6.8) | 63.8<br>(SD 11.1) | 7 | 49.8*<br>(SD 8.9) | 129.0**<br>(SD 24.3) |

results could be explained by the mode of stimulation used. Although the response to tetanic stimulation is a more sensitive indication of receptor occlusion than either the single twitch response or the train-of-four, tetanic stimulation may distort subsequent neuromuscular transmission (Lee and Katz, 1980) and increase the apparent degree of neuromuscular blockade. The train-of-four stimulus was chosen for this study since it is slightly more sensitive to receptor occlusion than is the single twitch (Lee, 1975). It also lacks the equivalent of post-tetanic distortion of the subsequent muscle response, and is therefore suitable for repeated application up to once every 12 s.

The use of volatile anaesthetic agents was avoided until after monitoring had been discontinued, because of the well documented interaction between volatile and neuromuscular blocking agents (Waud and Waud, 1979).

In this study, atracurium appeared to be a potent competitive neuromuscular blocking agent, and its effect at the neuromuscular junction is readily reversed. Although the onset of paralysis is rapid, with full peripheral paralysis occurring in just over 2 min, this is significantly slower than the action of suxamethonium. No significant changes in heart rate were seen and no perioperative problems encountered.

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## REFERENCES

Armstrong, J. E., Goat, V. A., and Loach, A. B. (1977). Measurement of neuromuscular blockade in man. *Anaesthesia*, 32, 480.

Dam, W. H., and Guldmann, N. (1961). Inadequate post-anaesthetic ventilation. *Anesthesiology*, 22, 699.

Harrison, P., and Feldman, S. A. (1981). Intubating conditions with Org NC 45. A preliminary study. *Anaesthesia*, 36, 874.

Hey, V. M. F. (1973). Relaxants for endo-tracheal intubation. *Anaesthesia*, 28, 32.

Hughes, R., and Chapple, D. J. (1980). Experimental studies with atracurium, a new neuromuscular blocking agent. *Br. J. Anaesth.*, 52, 238P.

—— —— (1981). The pharmacology of atracurium: a new competitive neuromuscular blocking agent. *Br. J. Anaesth.*, 53, 31.

Hunt, T. M., Hughes, R., and Payne, J. P. (1980). Preliminary studies with atracurium in anaesthetized man. *Br. J. Anaesth.*, 52, 238P.

Lee, C. M. (1975). Neuromuscular pharmacology. *Br. J. Anaesth.*, 54, 649.

—— Katz, R. L. (1980). Neuromuscular pharmacology. *Br. J. Anaesth.*, 52, 173.

Payne, J. P., and Hughes, R. (1981). Evaluation of atracurium in anaesthetized man. *Br. J. Anaesth.*, 53, 45.

Waud, B. E. and Waud, D. R. (1979). Effects of volatile anesthetics on directly and indirectly stimulated skeletal muscle. *Anesthesiology*, 50, 103.

## ATRACURIUM: SA RAPIDITE D'ACTION. UNE COMPARAISON AVEC LE SUXAMETHONIUM

### RESUME

Quarante sujets en bonne santé ont été choisis de façon aléatoire pour recevoir soit 0,6 mg kg$^{-1}$ d'atracurium, soit 1 mg kg$^{-1}$ de suxaméthonium. L'apparition de bloc neuromusculaire et le temps d'obtention d'une paralysie périphérique totale ont été mesurés en utilisant un stimulus par train de quatre répété toutes les 12 s. L'atracurium s'est montré un curare non dépolarisant puissant, d'action rapide. Cependant, l'obtention d'une paralysie périphérique complète a été plus longue qu'avec le suxaméthonium. Il n'y a pas eu de problèmes significatifs de décurarisation.

## ATRACURIUM, DIE GESCHWINDIGKEIT SEINES WIRKUNGSEINTRITTS IM VERGLEICH ZU SUXAMETHONIUM

### ZUSAMMENFASSUNG

Vierzig gesunde Patienten wurden randomisiert ausgewählt, um entweder 0,6 mg kg$^{-1}$ Suxamethonium zu erhalten. Der Beginn der neuromuskulären Blockade und die Zeit der vollen peripheren Blockade wurde gemessen, indem ein train of four-Stimulus alle 12 Sekunden gesetzt wurde. Atracurium schien ein potentes nicht-depolarisierendes Muskelrelaxans zu sein, mit schnellem Wirkungseintritt. Die volle periphere Lähmung jedoch trat später ein als bei Suxamethonium. Es wurden keine Schwierigkeiten bei der Antagonisierung oder in Zusammenhang mit der Operation beobachtet.

## ATRACURIO: SU VELOCIDAD INICIAL. UN ESTUDIO COMPARATIVO CON EL SUXAMETONIO

### SUMARIO

Se seleccionaron cuarenta pacientes sanos de forma aleatoria para administrárseles 0,6 mg kg$^{-1}$ de atracurio ó 1 mg kg$^{-1}$ de suxametonio. Se midió el inicio del bloqueo neuromuscular y el tiempo transcurrido hasta alcanzar una parálisis periférica total, haciendo uso de una serie de cuatro estímulos que se repitieron una vez cada 12 segundos. El atracurio pareció ser un potente relajante muscular de carácter no despolarizante que presentó una temprana actividad. Sin embargo, el tiempo necesario para alcanzer la parálisis periférica total fue mayor que en el caso del suxametonio. No se presentaron problemas de importancia en lo tocante a la recuperación.

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# EFFECTS OF PREMEDICATION ON DIPRIVAN INDUCTION

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SUMMARY

The effects of three premedication regimens were compared in 45 healthy patients in whom anaesthesia was induced with diprivan 2 mg $kg^{-1}$ i.v. Premedication with diazepam 10 mg orally and droperidol 2.5–5.0 mg and piritramide 7.5–15.0 mg i.m. resulted in less pain on injection and a more profound sleep from diprivan than premedication with diazepam 10 mg orally or no premedication. No differences in speed of induction were found when cessation of counting was used as a sign of unconsciousness. When the loss of eyelash reflex was used to define unconsciousness, the oral and i.m. premedication provided quicker induction after diprivan (39.3±2.9 s) than no premedication (53.7±3.0 s) ($P<0.05$) with no greater frequency of side-effects. Dose and rate of injection are the two most important factors influencing speed of induction.

Diprivan, ICI 35 868, a phenolic compound with the chemical structure 2,6-di-isopropyl phenol, has been used to induce anaesthesia i.v. (Kay and Rolly, 1977a, b; Kay and Stephenson, 1980; Rolly, Versichelen and Zubair, 1980; Rutter et al., 1980). Diprivan is dissolved in 16% cremophor EL and provided as a 1% solution. A dose of 2 mg $kg^{-1}$ is recommended for induction in unpremedicated patients (Briggs, Dundee and Clarke, 1981). The short duration of action is apparently caused by redistribution and rapid metabolism and the drug can be given by repeated injection or continuous infusion without cumulation (Adam, Glen and Hoyle, 1980; Kay and Adam, 1981). Induction time may be dependent on dose and speed of injection (Kay and Stephenson, 1980), a rapid injection time being advantageous. Because studies with the current formulation have been performed mainly on unpremedicated patients, we examined the effects of premedication on speed of induction and frequency of side-effects.

## METHODS

Forty-five healthy adults were studied after giving verbal consent at the time of the preoperative visit. They underwent elective surgery, did not abuse drugs or alcohol, had not recently been exposed to cremophor, had no history of atopy or allergy, and were not pregnant or nursing women. They were randomly assigned to one of three groups to receive no premedication (Group A), diazepam 10 mg orally (group B) or diazepam 10 mg orally plus droperidol 2.5–5.0 mg and piritramide 7.5–15 mg i.m. (group C) 60–90 min before induction of anaesthesia.

An i.v. infusion was inserted to a vein of the hand or forearm and arterial pressure, heart rate and respiratory rate were measured and recorded. Induction of anaesthesia was accomplished with diprivan 2 mg $kg^{-1}$ injected i.v. over 20 s. Patients began counting at the onset of injection and induction time was defined as the time which elapsed from the start of injection until cessation of counting. The time from the start of injection until the eyelash reflex disappeared was also measured. At the end of each minute for the next 3 min, arterial pressure, heart rate and respiratory rate were measured. Mean arterial pressure (m.a.p.) was calculated by the formula: (diastolic pressure + pulse pressure)/3. If apnoea occurred, its duration was recorded. Thereafter, conventional anaesthetics and myoneural blockers were administered. Any side-effects were recorded. If no spontaneous complaint of pain on injection occurred, patients were asked if they had pain, and, if so, where.

Comparisons of all measurements were analysed by a one-way analysis of variance except frequency of apnoea and pain on injection which were analysed by the Chi-square test (Runyon and Haber, 1977). Differences were considered significant when $P<0.05$.

## RESULTS

There were 10 females and five males in each group. A dose of diprivan 2 mg $kg^{-1}$ produced uncon-

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sciousness in all patients. Table I shows the ages, weights, induction times, frequency and duration of apnoea and frequency of pain on injection. The only significant difference between the groups occurred in the time from the start of injection until loss of the eyelash reflex, with a shorter time for patients in group C compared with those who had no premedication. There was a trend to a longer duration of apnoea as the amount of premedication increased. There was also a lesser frequency of pain on injection (20%) in the group receiving a narcotic for premedication, and all patients in this group who experienced pain had the infusion to the back of the hand. The back of the hand was the infusion site for two of seven who had pain on injection and no premedication, and seven of nine who had pain and received only diazepam. The overall frequency of pain on injection was 42%, but in the groups not receiving a narcotic it was 53%. Spontaneous complaints of pain were offered by four patients who received no premedication, seven who received only diazepam and only one who received a narcotic. The other complaints of pain were elicited by questioning the patient after the injection was completed.

Eight of the group who had no premedication and six of the group who had only diazepam (47% of both groups) began to waken before the end of the 3-min period of observation. Awakening did not occur in group C.

Significant changes in mean arterial pressure (m.a.p.) occurred within groups. M.a.p. decreased from control at each of the three subsequent observations in the group with no premedication and at 2 and 3 min after injection in group C. The only significant differences between groups (fig. 1) were for m.a.p. recorded at 2 and 3 min, which was less in group C than in the group which received no premedication. There were no significant changes in heart rate from control in any group. Heart rates recorded at 1 min were significantly less than control in group C.

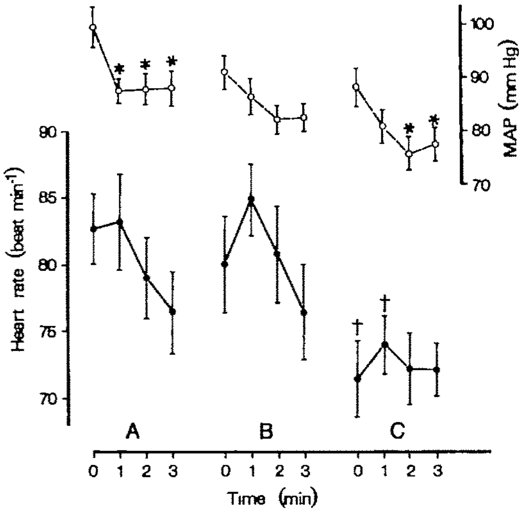

FIG. 1. Mean ± SEM for heart rate and mean arterial pressure (MAP) at control (0) and 1, 2, and 3 min after injection of diprivan. Group A received no premedication, group B diazepam 10 mg orally, and group C diazepam 10 mg orally plus droperidol 2.5–5.0 mg and piritramide 7.5–15.0 mg i.m. †$P<0.05$ *v.* the same time in groups A and B. *$P<0.05$ *v.* control. All other comparisons within the group or between groups are not significant ($P>0.05$).

## DISCUSSION

Premedication had no influence on the speed of induction when defined as time to cessation of counting. The mean times of 33.0–39.7 s are comparable to those reported by Major and others

TABLE I. *Demographic data and effects of premedication.* *$P<0.05$ *compared with no premedication. All other comparisons are not statistically significant. Except for the frequency of apnoea and pain on injection, all values shown are mean ± SEM*

| | Type of premedication | | |
|---|---|---|---|
| | None | Diazepam 10 mg | Diazepam 10 mg + droperidol 2.5–5.0 mg + piritramide 7.5–15 mg |
| Age (yr) | 32.3 ± 2.7 | 34.1 ± 2.4 | 34.5 ± 4.4 |
| Weight (kg) | 71.5 ± 2.9 | 72.2 ± 4.0 | 63.7 ± 2.0 |
| Stop counting (s) | 39.7 ± 2.4 | 33.0 ± 1.8 | 35.0 ± 2.1 |
| Loss of eyelash reflex (s) | 53.7 ± 3.0 | 47.7 ± 2.2 | 39.3 ± 2.9* |
| Apnoea (frequency, %) | 80 | 80 | 100 |
| Apnoea (duration, s) | 55.0 ± 5.6 | 61.3 ± 7.7 | 64.7 ± 11.0 |
| Pain on injection (frequency, %) | 41 | 60 | 20 |

(1981), Rolly, Versichelen and Zubair (1980) and Briggs, Dundee and Clarke (1981), and slightly faster than those reported by Rutter and colleagues (1980) and Rogers and others (1980). Time to the loss of eyelash reflex was influenced by the amount of premedication and was significantly less when the oral and i.m. premedication was given than when patients were unpremedicated. The loss of eyelash reflex may not be a good end-point with diprivan as a mask can be applied to the face and other anaesthetics introduced when the patient stops counting. Premedication with droperidol and a narcotic in addition to diazepam caused the sleep produced by diprivan 2 mg $kg^{-1}$ to be of sufficient duration to last for the 3-min period of observation. Another advantage of this premedication was the reduced frequency of pain on injection. It appears that pain on injection can be reduced in both its frequency and severity by previous administration of a narcotic and by injecting to the forearm rather than the hand.

Production of apnoea appears to be a feature of diprivan, since it occurred in 87% of the patients and lasted for the same amount of time regardless of the premedication used. A few patients were still apnoeic when they showed evidence of wakening from the injection.

Diazepam, droperidol and piritramide produced a slower control heart rate than the other premedications. Diprivan itself caused no change in heart rate from control in our study, which differs from an increase in heart rate reported by Major and colleagues (1981).

Most other investigators have reported, after diprivan, a decrease in arterial pressure of short duration which returned rapidly toward control. We also noted small decreases in mean arterial pressure which we considered to be clinically insignificant and which were returning toward control by the end of the 3-min observation period.

Although hypersensitivity reactions have been observed after injections of other drugs dissolved in cremophor, we observed no local or systemic reactions following injection of diprivan.

We conclude from this study that diprivan 2 mg $kg^{-1}$ administered i.v. over 20 s produces rapid loss of consciousness regardless of the premedication used. This confirms the dose and speed of injection are the most important factors in determining time of induction. Premedication with a narcotic and tranquillizer had the advantage of making the sleep produced by diprivan more profound and reduced the frequency of pain on injection which is the most disturbing side-effect reported with diprivan. We consider this amount of premedication to be safe because we found no increase in effects on circulation or respiration or other side-effects which were clinically significant.

## REFERENCES

Adam, H. K., Glen, J. B., and Hoyle, P. A. (1980). Pharmacokinetics in laboratory animals of ICI 35 868, a new intravenous induction agent. *Br. J. Anaesth.*, 52, 743.

Briggs, L. P., Dundee, J. W., and Clarke, R. S. J. (1981). Some observations with di-isopropyl phenol (ICI 35 868). *Br. J. Anaesth.*, 53, 183P.

Kay, B., and Adam, H. (1981). A dose–response relationship, and cumulation studies of Diprivan (ICI 35 868). *Br. J. Anaesth.*, 53, 118P.

——Rolly, G. (1977a). ICI 35 868, a new intravenous induction agent. *Acta Anaesthesiol. Belg.*, 28, 303.

————(1977b). ICI 35 868—The effect of a change of formulation on the incidence of pain after intravenous injection. *Acta Anaesthesiol. Belg.*, 28, 317.

——Stephenson, D. K. (1980). ICI 35 868 (Diprivan): a new intravenous anaesthetic. A comparison with Althesin. *Anaesthesia*, 35, 1182.

Major, E., Verniquet, A. J. W., Waddell, T. K., Savege, T. M., Hoffler, D. E., and Aveling, W. (1981). A study of three doses of ICI 35 868 for induction and maintenance of anaesthesia. *Br. J. Anaesth.*, 53, 267.

Rogers, K. M., Dewar, K. M. S., McCubbin, T. D., and Spence, A. A. (1980). Preliminary experience with ICI 35 868 as an intravenous induction agent. Comparison with Althesin. *Br. J. Anaesth.*, 52, 807.

Rolly, G., Versichelen, L., and Zubair, N. A. (1980). Use of ICI 35 868 as an anaesthetic induction agent. *Acta Anaesthesiol. Belg.*, 31, 241.

Runyon, R. D., and Haber, A. (1977). *Fundamentals of Behavioral Statistics*, 3rd edn, p. 288. Reading, Mass.: Addison-Wesley Pub. Co.

Rutter, D. V., Morgan, M., Lumley, J., and Owen, R. (1980). ICI 35 868 (Diprivan): a new intravenous induction agent. A comparison with methohexitone. *Anaesthesia*, 35, 1188.

## LES EFFETS DE LA PREMEDICATION SUR UNE INDUCTION AU DIPRIVANE

### RESUME

Les effets de trois sortes de prémédications ont été comparés chez 45 patients en bonne santé chez qui l'anesthésie était induite par le diprivane 2 mg $kg^{-1}$ i.v. La prémédication au diazépam 10 mg per os, associé au dropéridol 2,5–5 mg, et au piritramide 7,5–15 mg i.m., entraînait une diminution de la douleur lors de l'injection et une anesthésie plus profonde avec le diprivane que le diazépam 10 mg per os, ou l'absence de prémédication. Il n'a pas été noté de différences dans la vitesse d'induction en utilisant comme stigmate de la perte de conscience le fait que le patient arrête de compter. En utilisant la perte du réflexe palpébral pour définir la perte de conscience, la prémédication orale et i.m. permettrait une induction plus rapide ($P < 0,05$) après diprivane (39,3 ± 2,9 s) que l'absence de prémédication (53,7 ± 2,9 s), sans que la fréquence des effets secondaires soit plus grande. La posologie et la vitesse d'injection sont les deux facteurs les plus importants qui influencent la vitesse d'induction.

## DIE AUSWIRKUNGEN DER PRÄMEDIKATION AUF DIE EINLEITUNG MIT DIPRIVAN

### ZUSAMMENFASSUNG

Die Auswirkungen von drei Prämedikationsweisen wurden bei 45 gesunden Patienten, bei denen die Narkoseeinleitung mit Diprivan i.v. 2 mg kg$^{-1}$ durchgeführt wurde, verglichen. Prämedikation mit Diazepam 10 mg oral und Droperidol 2,5–5,0 mg und Piritramid 7,5–15,0 mg i.m. bewirkte geringeren Schmerz bei der Injektion und einen tieferen Schlaf auf Diprivan als mit Diazepam 10 mg oral oder ohne eine Prämedikation. Keine Unterschiede in der Geschwindigkeit der Einleitung wurden gefunden, wenn das Aufhören des Zählens als Zeichen für den Eintritt der Bewußtlosigkeit genommen wurde. Bei Verwendung des fehlenden Lidreflexes als Zeichen für den Eintritt der Bewußtlosigkeit ergab sich nach oraler und i.m. Prämedikation eine schnellere Narkoseeinleitung nach Gabe von Diprivan (39,3 ± 2,9 s) als ohne Prämedikation (53,7 ± 3,0 s) ohne daß mehr Nebenwirkungen auftraten. Die Dosis und die Injektionsrate sind die zwei wichtigsten Faktoren, die Einfluß auf die Geschwindigkeit der Narkoseeinleitung nehmen.

## EFECTOS DE LA PREMEDICACION SOBRE LA INDUCCION POR DIPRIVAN

### SUMARIO

Se compararon los efectos de diversos regímenes de premedicación en 45 pacientes a los que se indujo anestesia mediante 2 mg kg$^{-1}$ de diprivan administrados intravenosamente. La premedicación mediante 10 mg de diazepam administrados oralmente, asi como mediante 2,5–5,0 mg de droperidol y 7,5–15,0 mg de piritramide administrados intramuscularmente, produjeron un menor dolor durante la inyección y un sueño más profundo como consecuencia del diprivan que la producida por la premedicación con 10 mg de diazepam administrados oralmente o por la ausencia total de premedicación. No se hayaron diferencias en las velocidades de inducción cuando el cese de la cuenta se utilizó como signo de inconsciencia. Cuando se hizo uso de la pérdida de reflejos en el párpado para definir la inconsciencia, la premedicación oral e intramuscular aportó una inducción más rapida $P<0,05$) después del diprivan (39,3 ± 2,9 segundos) que lo obtenido sin premedicación alguna (53,7 ± 3,0 segundos) y una mayor frecuencia de efectos secundarios. La dosis y el régimen de la inyección son los dos factores más importantes que influencian la velocidad de la inducción.

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# EFFECT OF INJECTED VOLUME AND SPEED OF INJECTION ON THE SPREAD OF SPINAL ANAESTHESIA WITH ISOBARIC AMETHOCAINE

J. H. McClure, D. T. Brown, and J. A. W. Wildsmith

## SUMMARY

Amethocaine 10 mg in isobaric solution was injected intrathecally in 40 patients. Three volumes (1, 2 and 4 ml) of injection and two rates of injection (1 ml per 5 s and 1 ml per 10 s) were studied. Small volumes (1 and 2 ml) of the more concentrated solutions (1% and 0.5%) produced predictable blockade with spread restricted to the lower thoracic segments. Increasing the volume had little effect on the mean height of spinal blockade, but blockade was less predictable. Slowing the speed of injection of the largest volume (4 ml) partly counteracted this effect.

Previous studies (Brown et al., 1980; Wildsmith et al., 1981) demonstrated the advantages of the intrathecal administration of isobaric solutions of local anaesthetic drugs when a block restricted to the legs and perineum is required. In addition, these studies found that the administration of different volumes of solution did not affect the upper level of blockade. However, the results were obtained using 0.5% amethocaine and since the dose and the volume varied we decided to study the effects of the administration of a constant dose of amethocaine in different volumes and, at the same time, to compare two rates of injection.

## PATIENTS AND METHODS

Forty patients who were to undergo surgery to the legs or perineum under spinal anaesthesia consented to take part in the study. They were premedicated with temazepam 20 mg, placed in the lateral position and a standard mid-line lumbar puncture was performed, usually at the third interspace, using a 25-gauge needle. A solution containing amethocaine 10 mg was injected without barbotage and the patient turned supine for assessment. All injections were made by the same anaesthetist.

Amethocaine solutions were prepared by dissolving crystals in physiological saline immediately before injection, each patient having been assigned randomly to one of four groups of 10. Group A received amethocaine 10 mg in 1 ml (sp.gr (Specific Gravity at 25 °C) 1.0085), group B in 2 ml (sp.gr. 1.0077) and group C in 4 ml (sp.gr. 1.0065), each injected at the *rate* of 1 ml per 5 s. Group D also received 10 mg in 4 ml saline, but injected at 1 ml per 10 s.

Nerve blockade was assessed by an observer who was unaware of the volume and rate of injection used. The cephalad spread of analgesia and anaesthesia, and the degree of motor weakness in the legs, were assessed at 5-min intervals for 20 min. Analgesia was defined as the inability to appreciate pin-prick, and anaesthesia as the inability to appreciate touch. Motor weakness was graded as nil, partial or complete. Arterial pressure (by sphygmomanometry) and heart rate were recorded before the patient was positioned for lumbar puncture and at 5-min intervals after injection. The patients were visited at intervals after surgery until their legs had returned to normal and this time recorded as the duration of blockade.

Statistical analyses were made using *t* tests for paired or unpaired data, or $\chi^2$ as appropriate.

## RESULTS

The results are shown in table I and figure 1. The differences between the groups, in age, height and weight, were small although that in height between groups C and D was significant ($P < 0.05$).

Amethocaine 10 mg in 1 ml or 2 ml (groups A and B) produced virtually identical blockade. The mean upper level of analgesia was T11 and there were minimal differences in degree of motor blockade, duration of blockade and circulatory changes. There

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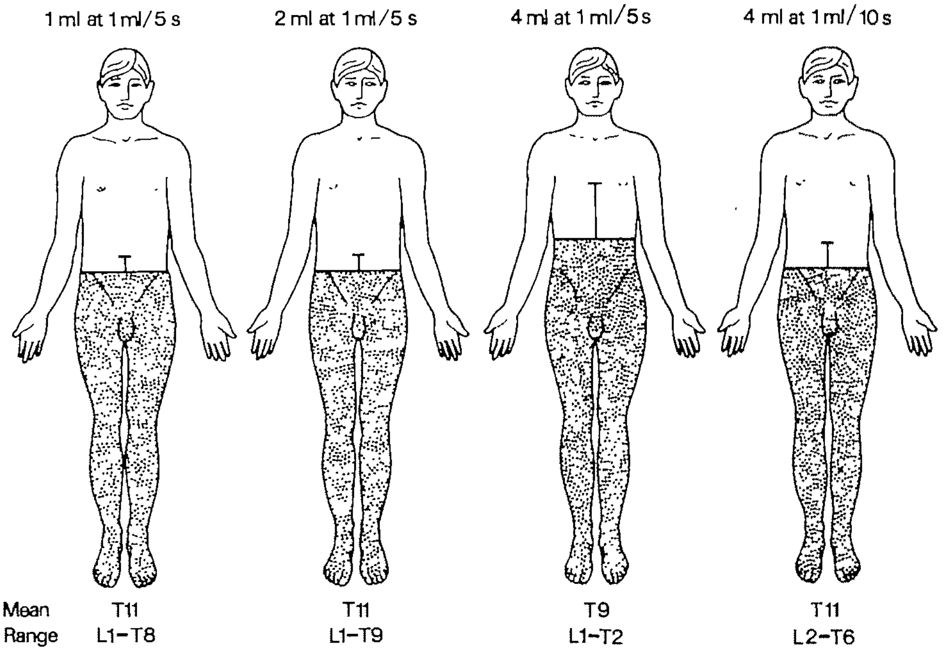

FIG. 1. Spread of blockade resulting from intrathecal injection of amethocaine crystals 10 mg dissolved in saline. The vertical bar represents the standard deviation of the group.

TABLE I. *Volume and duration of injection in four groups of patients receiving amethocaine 10 mg. Means ± SD of age, height and weight, levels of analgesia and anasthesia, motor block, duration, heart rate and systolic arterial pressure before and after 20 min are compared.* *P < 0.05 *for difference in height between these two groups;* § *one block of poor quality;* ¶ *four blocks of poor quality—one required supplementation;* † P < 0.05 *for change in heart rate;* ‡ *two patients received ephedrine and atropine, one atropine alone*

| | Group | | | |
|---|---|---|---|---|
| | A | B | C | D |
| Volume (ml) | 1 | 2 | 4 | 4 |
| Duration of injection (s) | 5 | 10 | 20 | 40 |
| Age (yr) | 45 ± 15 | 40 ± 13 | 36 ± 15 | 42 ± 12 |
| Height (cm) | 165 ± 12 | 168 ± 9 | 171 ± 7* | 163 ± 8* |
| Weight (kg) | 67 ± 20 | 69 ± 11 | 66 ± 12 | 65 ± 9 |
| Level of analgesia | T11 ± 1.7 | T11 ± 1.5 | T9 ± 4.1 | T11 ± 2.7 |
| Level of anaesthesia | T12 ± 2.0 | L1 ± 1.8 | T10 ± 4.1§ | L1 ± 3.6¶ |
| Motor block | 10 complete<br>— | 9 complete<br>1 partial | 9 complete<br>1 partial | 6 complete<br>4 partial |
| Duration (min) | 343 ± 80 | 342 ± 34 | 310 ± 56 | 322 ± 60 |
| Heart rate (beat $min^{-1}$) | | | | |
| Before | 80 ± 17 | 84 ± 13† | 77 ± 8‡ | 85 ± 16 |
| 20 min | 81 ± 15 | 79 ± 13 | 77 ± 7 | 82 ± 16 |
| Systolic AP (mm Hg) | | | | |
| Before | 130 ± 27 | 124 ± 14 | 130 ± 15‡ | 121 ± 20 |
| 20 min | 120 ± 28 | 110 ± 13 | 113 ± 16 | 111 ± 20 |

was an insignificant decrease in mean systolic arterial pressure in both groups and a significant decrease in mean heart rate in group B (mean decrease 5 beat $min^{-1}$; $P<0.05$). All these blocks were adequate for surgery.

In group C (4 ml at the same rate of injection, 1 ml per 5 s) the mean upper level of analgesia increased to T9. This level was not significantly different from groups A or B. However, there was a much wider scatter around this mean (table I). Three patients in this group required treatment for hypotension and bradycardia as a result of high thoracic blockade and in one other patient sensory blockade was too low for the proposed surgery. Duration of blockade was slightly less than in groups A and B. Circulatory values were similar to baseline at 20 min; three patients had received treatment by this time.

In group D amethocaine 4 ml was injected at the slower rate (1 ml per 10 s) and a mean upper level of analgesia was obtained at T11. This was similar to that obtained in groups A and B but the scatter of individual figures about this mean was wide. The changes in arterial pressure and heart rate were not significant and no patient required treatment. In four patients the sensory blockade was lower than that required for surgery and there was only partial motor blockade.

In all four groups the mean level of anaesthesia (total sensory loss) was less than two dermatomes lower than the level of analgesia. Scatter of individual levels about the means was wider in groups C and D than in groups A and B. The patients who were described as having low sensory blockade all responded to skin incision at the L1 level. Usually this lay between the upper levels of analgesia and anaesthesia and surgery was successfully completed in all except one patient in group D who required general anaesthesia.

## DISCUSSION

The specific gravities (at 25 °C) of the three volumes used are close to the range quoted for cerebrospinal fluid at this temperature (1.0075–1.0063). The mean heights of blockade using these and other isobaric amethocaine solutions studied (tables I and II) have all been to the lower thoracic segments regardless of volume, dose or posture of the patient.

The main effect of increasing the volume of the intrathecal injection was to increase the unpredictability of spread of the solution. Slowing the rate of injection countered this effect to some extent but the blocks were more variable than with the smaller volumes.

TABLE II. *Summary of results of injecting isobaric amethocaine obtained in previous studies. * Data from Wildsmith and others (1981); ** data from Brown and others (1980)*

| Dose (mg) | Volume (ml) | Position | Mean level |
|---|---|---|---|
| 5 | 1 | Sitting 5 min | T10* |
| 10 | 2 | Lateral 5 min | T10/T10* |
| 10 | 2 | Supine | T10** |
| 15 | 3 | Supine | T9** |

The lowest level of blockade obtained in each group was the same, L1 (fig. 1), and the clinical usefulness of the largest volume is, therefore, the same as the smaller volumes. However, using a volume of 4 ml increases the frequency of higher blockade and the risk of hypotension. T2 was the highest block seen in group C, T8 in group A and T9 in group B. No hypotension was seen when using 1 ml (group A) or 2 ml (group B) of solution.

Spinal anaesthesia with 0.5% plain bupivacaine has been described as "poorly predictable" (Cameron et al., 1981). This solution is near isobaric (sp. gr. 1.005 at 20 °C) and because it is of relatively low concentration is usually given in a volume of approximately 4 ml to ensure that an adequate dose is delivered. Cameron and colleagues (1981) injected 4 ml at a rate of 1 ml per 2 s and produced blockade distributed between T12 and T2 with a mean of T7. We have injected this same solution at 1 ml per 7.5 s and produced blocks that were more predictably limited to the lower thoracic segments, but occasional higher and lower blocks did occur (fig. 2).

Isobaric solutions are not affected by gravity (Wildsmith et al., 1981) and spread through the

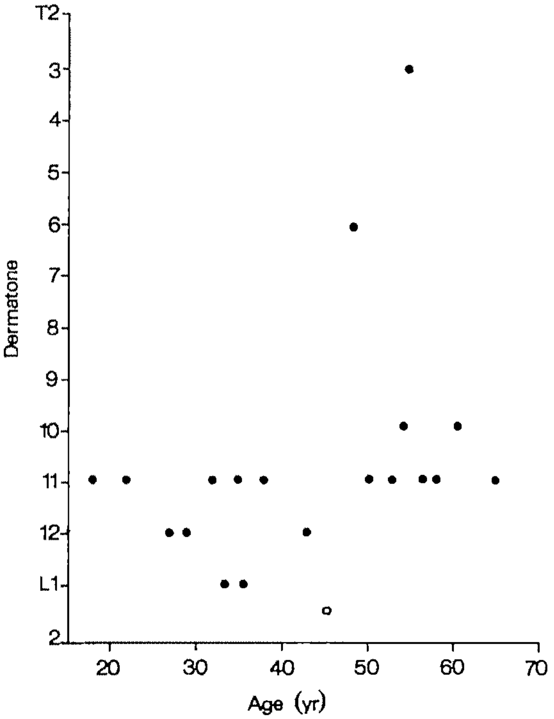

FIG. 2. Upper levels of analgesia with 4 ml of 0.5% plain bupivacaine injected over 30 s compared with age.

c.s.f., maybe by a combination of the currents set up by the injection and by diffusion of the drug. However, this does not explain why the spread of the larger volumes is less predictable. Possibly, spread of the larger volumes is also related to bulk displacement of c.s.f., the total volume of which might affect this displacement. Thus spread would be greater in the patients with a low c.s.f. volume. Cameron and colleagues (1981) suggested that a low c.s.f. volume could explain the increase in spread of spinal anaesthesia with 0.5% plain bupivacaine in the elderly.

We conclude that isobaric local anaesthetic solutions should be of sufficient concentration to allow an adequate dose to be given in a low volume. In this study we have shown that blockade resulting from the use of low volume isobaric solutions is predictable and limited to the legs and perineum and has minimal effects on the circulation.

### REFERENCES

Brown, D. T., Wildsmith, J. A. W., Covino, B. G., and Scott, D. B. (1980). Effect of baricity on spinal anaesthesia with amethocaine. *Br. J. Anaesth.*, 52, 589.

Cameron, A. E., Arnold, R. W., Ghoris, M. W., and Jamieson, V. (1981). Spinal analgesia using bupivacaine 0.5 per cent plain. Variations in the extent of block with patient age. *Anaesthesia*, 36, 318.

Wildsmith, J. A. W., McClure, J. H., Brown, D. T., and Scott, D. B. (1981). Effect of posture on the spread of isobaric and hyperbaric amethocaine. *Br. J. Anaesth.*, 53, 273.

## EFFET DU VOLUME INJECTE ET DE LA VITESSE D'INJECTION SUR LA DIFFUSION D'UNE RACHIANESTHESIE A L'AMETHOCAINE ISOBARE

### RESUME

De l'améthocaïne en solution isobare a été injectée en sous-dural chez 40 patients. Trois volumes (1, 2 et 4 ml) d'injection et deux vitesse d'injection (0,2 ml $s^{-1}$ et 0,1 ml $s^{-1}$) ont été étudiés. Les petits volumes (1 et 2 ml) des solutions les plus concentrées (1% et 0,5%) ont entrainé des blocs fiables dont l'étendue était limitée aux segments thoraciques inférieurs. L'augmentation de volume avait peu d'effet sur la hauteur moyenne du bloc spinal mais la qualité de ce bloc était moins fiable. Cet effet était partiellement contrecarré par un ralentissement de la vitesse d'injection pour le plus grand volume (4 ml).

## DIE AUSWIRKUNG DES INJIZIERTEN VOLUMENS UND DER INFEKTIONSGESCHWINDIGKEIT AUF DIE AUSBREITUNG DER SPINALANÄSTHESIE MIT ISOBARISCHEM AMETHOKAIN

### ZUSAMMENFASSUNG

Amethokain 10 mg in isobarer Lösung wurde bei 40 Patienten intrathekal injiziert. Drei Injektionsvolumina (1, 2 und 4 ml) und zwei-zeiten wurden untersucht (1 ml/5 s und 1 ml/10 s). Kleine Volumina der konzentrierteren Lösungen (1.0 und 0.5%) riefen vorhersehbare Blocks, deren Ausbreitung auf die unteren Thorakalsegmente beschränkt war, hervor. Eine Vergrösserung des Volumens wirkte sich wenig auf die durchschnittliche Höhe des Spinalblockes aus, die Wirkung war aber weniger steuerbar, was aber teilweise dadurch verhindert wurde, daß die Injektionsgeschwindigkeit beim größten Volumen (4 ml) langsamer war.

## EFECTO DEL VOLUMEN INYECTADO Y DE LA VELOCIDAD DE INYECCION EN LA DISPERSION DE LA ANESTESIA EN LA ESPINA DORSAL EFECTUADA CON AMEZCAINA ISOBARICA

### SUMARIO

Se inyectaron intratecalmente en 40 pacientes 10 mg de amezocaína en solución isobárica. Se estudiaron tres volúmenes (1, 2 y 4 ml) y dos regímenes de inyección (1 ml/5 s y 1 ml/10 s). Los volúmenes pequeños (1 y 2 ml) de las soluciones más concentradas (1% y 0,5%) produjeron un bloqueo predecible, quedando la dispersión reducida a los segmentos toråcticos inferiores. El incrementar el volumen ejerció poca influencia sobre la altura media del bloqueo, al tiempo que este fue menos predecible. El disminuir la velocidad de inyección del mayor volumen (4 ml) contrarrestó parcialmente este efecto.

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# PITUITARY FUNCTION FOLLOWING HYPOPHYSECTOMY FOR PAIN RELIEF

P. J. D. EVANS, J. W. LLOYD, R. A. MOORE AND R. F. SMITH

## SUMMARY

Eleven patients with bone pain from metastatic cancer had their pituitary function measured before and after the injection of absolute alcohol into the pituitary gland. Seven patients obtained relief of pain and the mean duration of benefit was 19.4 weeks. All the patients showed disturbance of pituitary function following the alcohol injection, but this disturbance varied from the loss of a single hormone to panhypopituitarism. There was no correlation between these changes and the occurrence of pain relief.

Pituitary destruction by the injection of absolute alcohol, as a treatment for painful metastases from hormone-dependent cancers, was developed by Moricca (1970, 1973, 1974a, b) after earlier workers had described various hormone-subtraction therapies as partially successful in controlling (but not providing analgesia for) the growth of the tumours. Since that time many workers have confirmed the value of the technique in providing good pain relief. Reports suggest that pain relief can be achieved in more than 70% of patients treated and that periods of relief ranging from several weeks to many months can occur (Corssen et al., 1977; Lipton et al., 1978; Lipton, 1981; Lloyd, Rawlinson and Evans, 1981; Roberts and Henderson, 1981). Unfortunately it is still not clear what mechanisms are involved in producing pain relief with this technique. Numerous theories have been advanced (Editorial, 1981) and include the suggestions that disturbance of pain pathways in the hypothalamus occurs, that pituitary destruction leads to a release of endorphin and that hormone changes, particularly oestrogen and progesterone, can influence sensory nerve conduction (Kawakami and Terashawa, 1967). Pituitary changes following chemical hypophysectomy have been recorded but they have failed to demonstrate a clear relation between gland destruction and the degree of pain relief (Williams et al., 1980). In a further attempt to quantify the endocrinological consequences of alcohol hypophysectomy, patients undergoing this treatment at the Oxford Regional Pain Relief Unit were investigated before and after therapy.

## METHOD

Patients with advanced metastatic cancer were considered for hypophysectomy if they met certain criteria. Only those patients who had painful bone metastases, had previously shown a response to hormone treatment and who had a long interval (greater than 6 months) from the onset of the disease to the development of severe pain were judged to be suitable.

A selective anterior hypophysectomy was performed with absolute alcohol 1 ml injected transsphenoidally through a fine-gauge needle. The treatment was performed in each patient under a light general anaesthetic; the detailed technique has been described previously (Lloyd, Rawlinson and Evans, 1981).

Pituitary function was tested on the day before hypophysectomy and repeated at 6 and 12 weeks after treatment. The method was that of Harsoulis and others (1973). Patients were fasted overnight but were allowed water to drink. Those already receiving corticosteroids were asked to withhold administration for 12 h before the study but we continued to give analgesics. The pituitary gland was then stimulated simultaneously by the i.v. administration of gonadatrophin-releasing hormone (100 μg of HRF, Ayerst), thyrotrophin releasing factor (200 μg of TRH, Roche) and insulin 0.05–0.15 u. $kg^{-1}$ to induce hypoglycaemic stress. The response to these stimuli was monitored at 30-min intervals for a period of 2 h. Plasma glucose

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estimations were made to confirm the adequacy of hypoglycaemic stress and a reduction in blood sugar to less than 3 mmol litre$^{-1}$ was considered essential.

The values obtained before operation were compared with the two sets taken after operation. The results were classified as *no response*, *normal* or *increased*. The appropriate normal responses for each test were as follows. Cortisol: peak value greater than 600 nmol litre$^{-1}$ and double the basal value. Growth hormone (GH): peak value greater than 20 mu. litre$^{-1}$. Prolactin: peak value greater than 1000 mu. litre$^{-1}$ and double basal value. Luteinizing hormone (LH): Twenty-minute peak 4–34 u. litre$^{-1}$ and 60-min value less than 20-min value. Thyroid stimulating hormone (TSH): Twenty-minute value 5–20 mu. litre$^{-1}$ and 60-min value less than 20-min value.

The results of treatment were assessed retrospectively. Pain relief was considered *good* if patients reported no pain or had a reduction of over 50% in narcotic analgesic consumption and *poor* if analgesic consumption remained unchanged and patients only reported slight relief of symptoms. Diabetes insipidus was confirmed by a daily urinary output exceeding 2.5 litre and by a reduction in output in response to the nasal administration of synthetic anti-diuretic hormone (DDAVP).

## RESULTS

Eleven patients suffering from cancer of either the breast or prostate had full pituitary investigations (table I). The mean age for the men was 66.6 yr and of the women was 52.3 yr. Good pain relief was achieved in seven patients and the mean duration of benefit was 19.4 weeks. The pituitary function tests, although expensive and time-consuming, were performed easily. Effective hypoglycaemia was induced in all 33 tests and it was only necessary to counteract an excessive effect on two occasions. Ten of the patients had been receiving corticosteroids before the study and all demonstrated a flat response to stress at the initial study. The remaining patient (10) demonstrated a normal increase in plasma cortisol after hypoglycaemia. Other abnormalities were detected in the preoperative studies. Two patients (7, 10) had increased values for LH and one patient (8) who had undergone alcohol hypophysectomy 8 months previously had, in addition, low values for both growth hormone and prolactin. A sustained increase in luteinizing hormone was observed in three patients (6, 7, 10). Two of these patients subsequently demonstrated the same phenomenon in the period after treatment. The remaining tests in the 11 patients at the preoperative investigation were normal.

Following the hypophysectomy a variable amount of gland destruction, as measured by pituitary function tests, was observed (table II). There were few differences between the observations at 6 weeks and 12 weeks. Three patients (1, 3, 7) showed some improvement in function and one patient (2) showed some deterioration at 12 weeks.

The extent of gland destruction did not correlate with the occurrence of pain relief. Of the seven patients with little or no pain, four had complete destruction of the anterior part of the gland and three had partial disturbance. Similarly, pain relief did not correlate with the presence of diabetes insipidus. There were two patients who developed this in each of the groups with and without pain relief. However, it did appear that total anterior gland destruction was associated with the development of diabetes insipidus. Three out of a total of five patients suffered this whereas only one patient developed this problem of six patients in whom partial

TABLE I. *Details of the 11 patients who had full pituitary function investigated before and after hypophysectomy*

| Patient No. | Age (yr) | Sex | Diagnosis | Site of pain | Pain relief | Duration |
|---|---|---|---|---|---|---|
| 1 | 45 | F | Carcinoma of breast | Hips, femur, spine and arm | Good | Over 8 months |
| 2 | 64 | M | Carcinoma of prostate | Spine, ribs and pelvis | Good | 4 months |
| 3 | 59 | F | Carcinoma of breast | Lumbar spine | Poor | — |
| 4 | 50 | F | Carcinoma of breast | Lumbar spine | Good | 7 weeks |
| 5 | 67 | M | Carcinoma of prostate | Lumbar spine and pelvis | Good | 9 weeks |
| 6 | 71 | M | Carcinoma of prostate | Thoracic and lumbar spine | Good | Over 7 months |
| 7 | 65 | F | Carcinoma of breast | Skull, neck and left femur | Poor | — |
| 8 | 65 | M | Carcinoma of prostate | Dorsal spine, pelvis and femur | Good | 7 months |
| 9 | 49 | F | Carcinoma of breast | Ribs and thoracic spine | Good | Over 4 months |
| 10 | 46 | F | Carcinoma of breast | Lumbar spine and right femur | Poor | — |
| 11 | 52 | F | Carcinoma of breast | Hips, ribs, neck and shoulders | Poor | — |

TABLE II. *Results of the pituitary function studies performed before and then 6 and 12 weeks after hypophysectomy. + = normal response to gland stimulation; R = increased values following stimulation and − = no function*

| Patient No. | Cortisol | | | Growth | | | Prolactin | | | LH | | | TSH | | | Diabetes Insipidus |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | pre | 6 wk | 12 wk | pre | 6 wk | 12 wk | pre | 6 wk | 12 wk | pre | 6 wk | 12 wk | pre | 6 wk | 12 wk | |
| 1 | − | − | − | + | + | + | + | + | + | + | − | + | + | + | + | None |
| 2 | − | − | − | + | − | − | + | − | − | + | + | − | + | − | − | None |
| 3 | − | − | − | + | − | − | + | − | + | + | R | R | + | + | + | None |
| 4 | − | − | − | + | − | − | + | + | + | + | − | − | + | − | − | None |
| 5 | − | − | − | + | − | − | + | − | − | + | − | − | + | − | − | Yes |
| 6 | − | − | − | + | − | − | + | − | − | R | − | − | + | − | − | Yes |
| 7 | − | + | − | + | + | − | − | + | + | R | R | R | + | + | + | None |
| 8 | − | − | − | − | − | − | − | − | − | + | − | − | + | − | − | None |
| 9 | − | − | − | + | − | − | + | + | + | + | − | − | + | + | + | None |
| 10 | + | − | − | + | − | − | + | + | + | R | R | R | + | + | + | Yes |
| 11 | − | − | − | + | − | − | + | − | − | + | − | − | + | − | − | Yes |

disturbance of the anterior part of the gland was observed.

Analysis of individual anterior pituitary hormone changes failed to show a conclusive relationship between pain relief and loss of function. Growth hormone and luteinizing hormone activity had both disappeared in six of the seven patients with analgesia, yet in three patients (1, 4, 9) prolactin activity remained and in two (1, 9) thyroid stimulating hormone function also remained.

In this small series all the male patients obtained pain relief while only three females were improved. This difference was not statistically significant (Fisher test), neither was there a correlation between the sex or type of cancer and the extent of gland destruction although two of the three patients (5, 6, 11) with complete destruction were male.

## DISCUSSION

This study confirms once again that effective pain relief can be produced in patients suffering from advanced cancer, by the injection of absolute alcohol into the pituitary gland. The assessment of pituitary hormone production demonstrated that destruction of the gland occurred. Yet it was unpredictable, varied from the disturbance of one or two anterior pituitary hormones to panhypopituitarism and was not related to the production of pain relief.

It had been the practice at the Oxford Pain Relief Unit to perform a selective anterior hypophysectomy to reduce the frequency of the disabling complication of diabetes insipidus. Clearly the results of the endocrine studies show that this was not always achieved. Three of the patients with the complication had loss of all anterior pituitary function yet the fourth (10) had only minimal disturbance of the anterior gland. It appeared that only those patients who suffered partial anterior gland dysfunction were unlikely to develop this complaint. One patient (8) who lost all anterior pituitary function did not develop diabetes insipidus, but he was unusual in that there was already some gland damage from a previous alcohol injection.

Pain relief was not related to the disappearance of any particular anterior pituitary hormone, but some hormones were more sensitive than others to the effects of alcohol injection. The production of growth hormone was most sensitive and this is consistent with the observations of Moricca (1977). Thyroid stimulating hormone and luteinizing hormone were least sensitive and if a test was necessary to assess the extent of gland destruction, in those patients not developing diabetes insipidus, then a stimulation test for either of these hormones would provide most information. Testing for pituitary reserve of both these hormones is easily achieved without the need to resort to a full pituitary function test.

Williams and others (1980) have studied pituitary function before and after operation in a small group of patients undergoing alcohol hypophysectomy. They also failed to observe any correlation between the production of pain relief and the degree of gland destruction. Even combining their results with those of this study (total sample 22 patients) failed to alter the conclusions. For the combined data pain relief was not related to the extent of anterior gland destruction, the loss of a particular hormone or the production of diabetes insipidus. In addition the duration of pain relief was compared with the extent of gland destruction, but again there was no correlation (one-way analysis of variance). This disassociation between gland destruction and pain relief has been reported by others (Moricca, 1974; Levin et al., 1978).

Miles and Lipton (1976) demonstrated that tracking of both dye and contrast media into the hypothalamus occurs during hypophysectomy. They naturally reasoned that, if there was no relationship between pituitary destruction and pain relief, then perhaps alcohol damage to the hypothalamus might be responsible. Yet Levin and others (1978) suggest that destruction of pathways in the hypothalamus would be unlikely to relieve pain as the available evidence indicates that it is stimulation of inhibitory pathways that is required to control pain appreciation.

All the patients treated in this study had bone pain. This is likely to have arisen from a number of causes, for example pressure effects stretching periosteum, bone rarefaction precipitating pathological fractures and necrotic tissue producing a chronic inflammatory reaction. All of these mechanisms would be likely to stimulate the production of prostaglandins and it is possible that if the injection of alcohol had an inhibitory effect on synthesis then it might explain the increasing pain relief observed after hypophysectomy. This would not, of course, explain the immediate relief observed in some patients and perhaps for this the release of large quantities of beta-endorphin remains the most tenable theory. The work of Fujita and others (1980) lends credence to this idea. They observed significant increases in pain thresholds in patients following hypophysectomy as well as gross increases in adrenocorticotrophic hormone (ACTH). Yanagida and others (1979) demonstrated similar changes in pain appreciation and they noted that in part this increase in pain threshold could be reversed by naloxone. This led them to suggest that an increase in beta-endorphin was the mediator of the pain relief.

We conclude that injection of alcohol into the pituitary gland may affect indirectly a number of hormone mechanisms apart from the obvious ones of the adenohypophysis. The failure to demonstrate a relationship between gland destruction and pain relief probably reflects the current inability to measure readily many of these hormones and neurotransmitters.

## REFERENCES

Corssen, G., Holcomb, M. C., Moustapha, I., Langford, K., Vitek, J. J., and Ceballos, R. (1977). Alcohol-induced adenolysis of the pituitary gland: a new approach to control of intractable cancer pain. *Anesth. Analg. Cleve.*, **56**, 414.

Editorial (1981). Pituitary ablation for pain relief. *Lancet*, **1**, 1348.

Fujita, T., Kitani, Y., Tozawa, R., and Takeda, F. (1980). Mode of pain relief on recrudescence after alcohol hypophysectomy; in *Abstracts Seventh World Congress of Anaesthesiologists, Hamburg FRG* (eds G. Rugheimer, J. Wawersteik and M. Zindler). Amsterdam: Excerpta Medica.

Harsoulis, P., Marshall, J. C., Kuku, S. F., Burke, C. W., London, D. R., and Fraser, T. R. (1973). Combined test for assessment of anterior pituitary function. *Br. Med. J.*, **4**, 326.

Kawakami, M., and Terashawa, E. (1967). Differential control of sex hormones and oxytocin in evoked potentials in the hypothalamus and midbrain reticular formation. *Jap. J. Physiol.*, **17**, 65.

Levin, A. B., Benson, R. C., Katz, J., and Nilsson, T. (1978). Chemical hypophysectomy for relief of bone pain in carcinoma of the prostate. *J. Urology*, **119**, 517.

Lipton, S. (1981). Intractable pain—the present position. *Ann. R. Coll. Surg.*, **63**, 157.

—— Miles, J., Williams, N., and Bark-Jones, N. (1978). Pituitary injection of alcohol for widespread cancer pain. *Pain*, **5**, 73.

Lloyd, J. W., Rawlinson, W. A. L., and Evans, P. J. D. (1981). Selective hypophysectomy for metastatic pain. *Br. J. Anaesth.*, **53**, 1129.

Miles, J. B., and Lipton, S. (1976). Mode of action by which pituitary alcohol injection relieves pain; in *Advances in Pain Research and Therapy* (eds J. J. Bonica and A. Fessard), Vol. 1, p. 867. New York: Raven Press.

Moricca, G. (1970). In *Progress in Anesthesiology* (ed. T. B. Boulton), p. 266. Amsterdam: Excerpta Medica.

—— (1973). In *Anesthesiology* (ed. M. Miyazaki), p. 271. Amsterdam: Excerpta Medica.

—— (1974a). In *Recent Advances in Pain* (ed. J. J. Bonica), p. 313. Springfield: Thomas.

—— (1974b). Chemical hypophysectomy for cancer pain; in *Advances in Neurology* (ed. J. J. Bonica), p. 707. New York: Raven Press.

—— (1977). Pituitary neuroadenolysis in the treatment of intractable pain from cancer; in *Persistent Pain, Modern Methods of Treatment* (ed. S. Lipton), p. 149. London: Academic Press, and New York: Grunne & Stratton.

Roberts, M. T. S., and Henderson, R. S. (1981). Pituitary fossa injection with alcohol for widespread cancer pain. *N. Z. Med. J.*, **93**, 1.

Williams, N. E., Miles, J. B., Lipton, S., Hipklin, L. J., and Davis, J. C. (1980). Pain relief and pituitary function following injection of alcohol into the pituitary fossa. *Ann. R. Coll. Surg.*, **62**, 203.

Yanagida, H., Corssen, G., Ceballos, R., and Strong, E. (1979). Alcohol induced pituitary adenolysis; How does it control intractable cancer pain. *Anesth. Analg. (Cleve.)*, **58**, 279.

## LA FONCTION HYPOPHYSAIRE APRES HYPOPHYSECTOMIE POUR TRAITEMENT DE LA DOULEUR

### RESUME

Onze patients souffrant de douleurs osseuses métastatiques ont eu une étude de leur fonction hypophysaire avant et après injection d'alcool absolu dans la glande pituitaire. Sept patients ont été soulagés et la durée moyenne d'analgésie a été de 19,4 semaines.

Tous les patients avaient une fonction pituitaire perturbée après l'injection d'alcool, mais cette perturbation allait de la perte d'une seule hormone au panhypopituitarisme. Il n'y avait pas de corrélation entre ces perturbations et la survenue d'une analgésie.

## DIE FUNKTION DER HYPOPHYSE NACH HYPOPHYSEKTOMIE ZUR SCHMERZBEKÄMPFUNG

### ZUSAMMENFASSUNG

Bei elf Patienten, die wegen Krebsmetastasen am Knochen Schmerzen litten, wurde die Hypophysenfunktion vor und nach der Injektion von reinem Alkohol in die Hypophyse gemessen. Bei sieben Patienten besserten sich die Schmerzen, wobei die Besserung im Durchschnitt 19,4 Wochen anhielt. Alle Patienten zeigten eine Störung der Hypophysenfunktion nach der Alkoholinjektion. Doch die Störungen wechselten vom Ausfall nur eines Hormons bis zum totalen Ausfall der Hypophyse. Es bestand keine Korrelation zwischen diesen Funktionsstörungen und der Schmerzerleichterung.

## FUNCIONAMIENTO DE LA PITUITARIA A RAIZ DE LA HIPOFISECTOMIA PARA FINES DE ALIVIO DEL DOLOR

### SUMARIO

Se midió el funcionamiento de la pituitaria en once pacientes con dolor de huesos causado por cancer metastático, antes y después de inyectárseles una inyección de alcohol puro dentro de la glándula pituitaria. Siete de los pacientes experimentaron alivio del dolor y la duración media de aquel fue de 19,4 semanas. Todos los pacientes mostraron perturbación del funcionamiento de la pituitaria a raiz de la inyección de alcohol, pero esta perturbación osciló entre la pérdida de sólo una hormona y el panhipopituitarismo. No hubo correlación alguna entre estos cambios y el que hubiera habido alivio del dolor.

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# ZOMEPIRAC, PLACEBO AND PARACETAMOL/DEXTROPROPOXYPHENE COMBINATION COMPARED IN ORTHOPAEDIC POSTOPERATIVE PAIN

P. J. D. EVANS, H. J. MCQUAY, M. ROLFE, G. O'SULLIVAN, R. E. S. BULLINGHAM AND R. A. MOORE

## SUMMARY

Zomepirac sodium was studied at two doses (50 or 100 mg) against a dextropropoxyphene/paracetamol combination and placebo in a double-blind randomized trial. One hundred and twenty patients with moderate to severe pain after minor orthopaedic surgery were studied. Zomepirac 50 mg showed consistently significant analgesic effect compared with placebo. The standard analgesic was significantly different from placebo only for pain relief and observer global assessment. Zomepirac 100 mg showed no statistically significant difference from placebo on any analgesic measurement. Zomepirac 50 mg was at least therapeutically equivalent to the dextropropoxyphene/paracetamol combination and may have advantages with regard to toxicity.

The oral route provides a simple method of drug administration. In a search to find an effective analgesic readily absorbed from the gastrointestinal tract with minimal central nervous system depression, a number of non-opiate drugs have been investigated. Zomepirac, sodium 5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrole-2-acetate dihydrate (throughout the paper zomepirac doses all refer to this sodium salt), is a recently introduced prostaglandin biosynthesis inhibitor. Testing in animals has shown that oral zomepirac may be as potent as subcutaneous morphine (Pruss et al., 1980).

In man, a number of studies have demonstrated that zomepirac is an effective analgesic for the control of moderate to severe postoperative pain (Forrest, 1980; Wallenstein et al., 1980). A single oral dose of zomepirac 100 mg seems to be as effective as 8–16 mg of i.m. morphine, and 50 mg was as effective as 650 mg of aspirin in a dental model (Cooper, 1980a).

The present study was undertaken to assess the efficacy of zomepirac for the control of postoperative pain following minor orthopaedic surgery. The drug was compared at two doses, 50 and 100 mg, with a standard combined analgesic preparation containing dextropropoxyphene and paracetamol (Cosalgesic) and a placebo.

## METHODS

This study was designed as double-blind, single-dose and non-crossover. Ethics committee approval was obtained to study patients undergoing elective minor orthopaedic surgery of the upper and lower limbs at the Nuffield Orthopaedic Centre, Oxford.

One hundred and twenty fit patients were included in the trial. They were selected provided that they were aged 16 yr or more and weighed between 45 and 90 kg. They were excluded if suffering from severe renal, hepatic or cardiac disease, marked ventilatory impairment as a result of underlying respiratory disease or if they had been receiving regular doses of narcotic analgesics. In addition, patients with a recent history of gastrointestinal bleeding or peptic ulceration were excluded. Women of child bearing age if pregnant or not using a reliable method of contraception with the last menstrual period more than 10 days previously were also excluded.

A standard anaesthetic technique was used. Two hours before operation they each received diazepam 10 mg orally. At induction of anaesthesia atropine 0.6 mg was given i.v. as prophylaxis for intraoperative bradycardia and this was followed by thiopentone 5 mg $kg^{-1}$ i.v. Anaesthesia was maintained with spontaneous breathing from the Bain system of 33% oxygen in nitrous oxide with 1–3% halothane and a total gas flow of 150 ml $kg^{-1}$ through a face-mask.

After operation all patients were transferred to a

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recovery ward where they remained until the following morning. They were looked after solely by the trained, full-time nurse observer (M.R.). Pain was assessed using a four-point scale (none = 0, mild = 1, moderate = 2 and severe = 3). Pain of moderate or severe intensity occurring within 2 h of recovery from anaesthesia was treated with the test medication. The treatments were block randomized in groups of 12 and were identical in appearance. Active treatments contained either zomepirac (Zomax, Ortho Pharmaceutical Ltd, Saunderton) or dextropropoxyphene 32.5 mg and paracetamol 325 mg (Cosalgesic, Cox-Continental Ltd, West Sussex). Each treatment consisted of four tablets representing one of the following: Cosalgesic = 2 Cosalgesic + 2 placebo zomepirac 50 mg; zomepirac 100 mg = 2 placebo Cosalgesic + 2 zomepirac 50 mg; zomepirac 50 mg = 2 placebo Cosalgesic + 1 zomepirac 50 mg + 1 placebo zomepirac 50 mg; placebo = 2 placebo Cosalgesic + 2 placebo zomepirac 50 mg. Tablets and containers were packed by Ortho Pharmaceutical.

Before receiving the test medication, measurements of pain intensity, sedation (0 = alert, 1 = mildly drowsy, 2 = moderately drowsy and 3 = asleep), heart rate, arterial pressure and respiratory rate were made. These were repeated with measurements of pain relief (0 = none, 1 = slight, 2 = moderate, 3 = good and 4 = complete) at 0.5, 1, 2, 3 and 4 h. In addition, visual analogue scale measurements of pain intensity, pain relief and mood were made, using 10-cm lines, at 0, 1, 2, 3 and 4 h, together with an assessment of the pain intensity on a seven-word verbal rating scale (no pain, just noticeable, mild, weak, moderate, strong, severe and excruciating; same random word display to each patient, scored 0–7 in this order). Volunteered side-effects and their severity were noted. Any medication required before the patient left the recovery room the following morning was recorded. If no pain relief was obtained from the test medication after 1 h or if the pain intensity reverted to initial values, papaveretum was administered i.m. At the end of the study period the global impression of therapy was scored by the patient and the observer on a five-point scale (1 = excellent, 2 = very good, 3 = good, 4 = fair and 5 = poor). Patients who received the medication and who subsequently vomited remained in their appropriate trial group and received either metaclopramide 10 mg or perphenazine 2.5 mg i.m.

The sum of pain intensity difference (SPID) and total pain relief (TOTPAR), peak pain intensity difference (PEAK PID) and peak pain relief (PEAK REL) were calculated by standard procedures (Wallenstein and Houde, 1975) with and without stratification of the initial pain intensity values, and with stratification by site of operation. The visual analogue equivalents, VAS-SPID for pain intensity, VAS-TOTPAR for pain relief, and the verbal rating scale equivalent for pain intensity, VRS-SPID, were derived in the same way as for SPID and TOTPAR. Patients who required remedication before the end of the 4-h study period were ascribed initial values of pain intensity and a pain relief score of zero (Lasagna, 1980).

The overall sedation and mood measures, AUC SEDATION and AUC MOOD were calculated as the area under the curves of the effect *v.* time data by a trapezoidal formula.

Statistical analysis for the analgesic measures and demographic data was by the Kruskal–Wallis one-way analysis of variance and Student's *t* test. The frequency of side-effects and time to next analgesia were analysed by the chi-square test.

## RESULTS

The patients in this study all had minor orthopaedic operations. There were 30 patients in each of the four study groups and the basic data are shown in table I. The groups did not differ significantly for age, weight, height or sex ratio and the spectrum of operative procedures was consistent between each of the four groups. The duration of surgery was, however, significantly longer for the zomepirac 100 mg group than for placebo, and longer for both zomepirac groups than for Cosalgesic. There was, however, no difference between the two zomepirac groups.

The total and stratified SPID and TOTPAR values obtained for each group are shown in table II. The Kruskal–Wallis analysis of variance was significant for SPID overall ($P < 0.05$), for patients with an initially moderate pain intensity ($P < 0.02$) and those with leg operations ($P < 0.05$). Zomepirac 50 mg was significantly better than placebo ($P < 0.01$, *t* test). Zomepirac 50 mg was also significantly better than placebo for patients with an initially severe pain intensity and those with leg operations. Zomepirac 50 mg could not be differentiated statistically from either zomepirac 100 mg or Cosalgesic.

For TOTPAR, analysis of variance showed no overall differences, although both zomepirac 50 mg

TABLE I. *Patient data (mean ± SEM). Significant differences: 1 = from placebo,* $P < 0.01$*; 2 = from Cosalgesic,* $P < 0.001$*; 3 = from Coalgesic,* $P < 0.05$*; Student's* t *test*

| | Group | | | |
|---|---|---|---|---|
| | Cosalgesic | Zomepirac 100 mg | Zomepirac 50 mg | Placebo |
| Number | 30 | 30 | 30 | 30 |
| Age (yr) | 46.0 ± 3.1 | 43.8 ± 3.0 | 39.4 ± 3.0 | 38.3 ± 2.3 |
| Weight (kg) | 69.5 ± 1.7 | 70.5 ± 2.1 | 67.6 ± 1.8 | 66.1 ± 1.9 |
| Height (cm) | 166.9 ± 1.6 | 170.2 ± 2.0 | 168.6 ± 1.6 | 166.9 ± 2.1 |
| Surface area ($m^2$) | 1.77 ± 0.03 | 1.81 ± 0.04 | 1.76 ± 0.03 | 1.74 ± 0.04 |
| Sex ratio (M:F) | 12:18 | 14:16 | 15:15 | 14:16 |
| Surgery time (min) | 17.6 ± 2.0 | 32.1 ± $2.8^{1,2}$ | 25.6 ± $3.3^{3}$ | 21.1 ± 2.9 |
| Operative procedure: | | | | |
| Carpal tunnel release: | 6 | 3 | 4 | 9 |
| Meniscectomy: | 3 | 6 | 5 | 5 |
| Other knee operations: | 4 | 3 | 2 | 2 |
| Keller's: | 4 | 5 | 9 | 2 |

TABLE II. *Total and stratified SPID and TOTPAR scores (mean ± SEM). Significant differences on Kruskal–Wallis analysis of variance:* †$P < 0.05$, ††$P < 0.02$*. Significant differences from placebo:* *$P < 0.05$, **$P < 0.02$, ***$P < 0.01$*, Student's* t *test*

| | Group | | | |
|---|---|---|---|---|
| | Cosalgesic | Zomepirac 100 mg | Zomepirac 50 mg | Placebo |
| SPID | | | | |
| Overall† | 3.25 ± 0.60<br>(*n* = 30) | 2.73 ± 0.53<br>(*n* = 30) | 4.35 ± 0.58***<br>(*n* = 30) | 2.08 ± 0.40<br>(*n* = 30) |
| Severe | 3.58 ± 1.15<br>(*n* = 12) | 2.93 ± 0.81<br>(*n* = 15) | 5.25 ± 0.91*<br>(*n* = 16) | 2.50 ± 0.75<br>(*n* = 11) |
| Moderate†† | 3.03 ± 0.67<br>(*n* = 18) | 2.53 ± 0.69<br>(*n* = 15) | 3.32 ± 0.62<br>(*n* = 14) | 1.84 ± 0.48<br>(*n* = 19) |
| Arms | 3.32 ± 0.96<br>(*n* = 17) | 3.50 ± 0.88<br>(*n* = 12) | 4.94 ± 1.01<br>(*n* = 8) | 2.53 ± 0.65<br>(*n* = 15) |
| Legs† | 3.15 ± 0.64<br>(*n* = 13) | 2.22 ± 0.64<br>(*n* = 18) | 4.14 ± 0.71***<br>(*n* = 22) | 1.63 ± 0.47<br>(*n* = 15) |
| TOTPAR | | | | |
| Overall | 7.37 ± 1.02*<br>(*n* = 30) | 6.15 ± 0.92<br>(*n* = 30) | 7.90 ± 0.87**<br>(*n* = 30) | 4.70 ± 0.85<br>(*n* = 30) |
| Severe | 5.50 ± 1.62<br>(*n* = 12) | 4.97 ± 1.16<br>(*n* = 15) | 7.41 ± 1.24<br>(*n* = 16) | 4.14 ± 1.15<br>(*n* = 11) |
| Moderate | 8.61 ± 1.27*<br>(*n* = 18) | 7.33 ± 1.39<br>(*n* = 15) | 8.46 ± 1.23*<br>(*n* = 14) | 5.03 ± 1.18<br>(*n* = 19) |
| Arms | 7.27 ± 1.47<br>(*n* = 17) | 7.63 ± 1.70<br>(*n* = 12) | 9.25 ± 1.61<br>(*n* = 8) | 5.77 ± 1.39<br>(*n* = 15) |
| Legs | 7.50 ± 1.43*<br>(*n* = 13) | 5.17 ± 1.00<br>(*n* = 18) | 7.41 ± 1.03**<br>(*n* = 22) | 3.63 ± 0.95<br>(*n* = 15) |

and Cosalgesic—but not zomepirac 100 mg—were significantly better than placebo ($P < 0.05$, *t* test). Zomepirac 50 mg was also significantly better than placebo for leg operations, as was Cosalgesic for leg operations and initally moderate pain intensities. Again, none of the treatment groups could be distinguished from another.

The results for the analgesic measurements performed with the visual analogue scales are shown in table III. The peak intensity and relief scores, the verbal rating scores, sedation and global assessments are also recorded. Zomepirac 50 mg was significantly better than placebo, but not zomepirac 100 mg or Cosalgesic, for PEAK PID, PEAK REL, VAS-SPID, VRS-SPID, VAS-TOTPAR, AUC MOOD and global assessment by the nurse-observer. Cosalgesic was significantly better than placebo for VAS-TOTPAR, AUC MOOD and global assessment by the patient. Kruskal–Wallis analysis of variance supported these findings for VAS-TOTPAR ($P < 0.05$) and AUC MOOD ($P < 0.02$).

All three analgesic preparations provided analgesia for a median duration in excess of 4 h (table IV) and the number of patients requiring remedication by 4 h was significantly less than placebo in all three treatment groups ($P < 0.05$, chi-square test).

The reported side-effects and changes in vital signs are shown in table V. There was no difference between the groups for side-effects. There were no patients who showed a decrease in respiratory rate to less than 10 b.p.m. or whose systolic arterial pressure decreased to less than 80 mm Hg. However, the number of patients in the groups treated with zomepirac who developed a decrease in heart rate of 20 beat min$^{-1}$ or more was significantly greater than in the placebo group ($P < 0.05$, chi-square analysis).

## DISCUSSION

This trial shows a statistical separation of a treatment group from placebo for SPID and VAS-TOTPAR using the Kruskal–Wallis analysis of variance. The zomepirac 50 mg group showed significant differences from placebo on *t* testing within

TABLE III. *Visual analogue and peak intensity and relief scores (mean ± SEM). Significant differences on Kruskal–Wallis analysis of variance:* †P < *0.05,* ††P < *0.02. Significant differences from placebo:* **P < *0.02,* ***P < *0.01, Student's* t *test*

| | Group | | | |
|---|---|---|---|---|
| | Cosalgesic (*n* = 30) | Zomepirac 100 mg (*n* = 30) | Zomepirac 50 mg (*n* = 30) | Placebo (*n* = 30) |
| PEAK PID | 1.20 ± 0.18 | 1.23 ± 0.16 | 1.60 ± 0.16*** | 0.93 ± 0.16 |
| PEAK REL | 2.40 ± 0.30 | 2.37 ± 0.27 | 2.83 ± 0.24*** | 2.07 ± 0.24 |
| VAS-SPID | 99 ± 18 | 79 ± 20 | 118 ± 19** | 62 ± 15 |
| VRS-SPID | 6.8 ± 1.3 | 6.2 ± 1.4 | 9.5 ± 1.4*** | 4.6 ± 0.9 |
| VAS-TOTPAR† | 212 ± 30 | 169 ± 26 | 231 ± 25*** | 132 ± 25 |
| AUC MOOD †† | 270 ± 18*** | 230 ± 17 | 269 ± 13*** | 218 ± 16 |
| AUC sedation | 2.22 ± 0.58 | 1.47 ± 0.45 | 2.27 ± 0.57 | 2.45 ± 0.62 |
| Global assessment | | | | |
| Patient | 2.83 ± 0.26** | 3.13 ± 0.24 | 3.03 ± 0.21 | 3.63 ± 0.22 |
| Sister | 3.37 ± 0.24 | 3.63 ± 0.23 | 3.10 ± 0.22*** | 3.93 ± 0.19 |

TABLE IV. *Measures of duration of analgesia. Significance difference from placebo. Chi-square test:* *P < *0.05*

| | Group | | | |
|---|---|---|---|---|
| | Cosalgesic (*n* = 30) | Zomepirac 100 mg (*n* = 30) | Zomepirac 50 mg (*n* = 30) | Placebo (*n* = 30) |
| Median time to next analgesic (min) | 308 | 245 | 310 | 148 |
| No. patients remedicated by 240 min | 12* | 13* | 9* | 20 |

TABLE V. *Side effects. Significant difference from placebo, zomepirac 50 and 100 mg combined data, Chi-square test:* **$P<0.05$*

| | Group | | | |
|---|---|---|---|---|
| | Cosalgesic ($n=30$) | Zomepirac 100 mg ($n=30$) | Zomepirac 50 mg ($n=30$) | Placebo ($n=30$) |
| Dizziness | 1 | 1 | 0 | 0 |
| Depression | 0 | 1 | 0 | 0 |
| Headache | 5 | 4 | 5 | 5 |
| Thirst | 0 | 1 | 1 | 1 |
| Nausea | 1 | 1 | 1 | 0 |
| Confused | 0 | 1 | 0 | 0 |
| Decrease in heart rate $>20$ beat $\text{min}^{-1}$ | 9 | 14* | 15* | 7 |

these measures. Furthermore, zomepirac 50 mg showed highly significant *t* test differences from placebo on all other analgesic measures. The notable result is that the greater zomepirac dose of 100 mg was not distinguished from placebo in this trial, under circumstances in which the 50-mg dose was. Fifteen separate indices of analgesic effect were considered. Consistently the various measures showed a rank order of: placebo < zomepirac 100 mg < Cosalgesic < zomepirac 50 mg. This same rank order was obtained for almost all the measures. The nurse observer requires some degree of agreement within the various assessments and so these measures are not statistically independent. The statistical significance of the rank ordering cannot consequently be given. However, the consistency of the ranking provides evidence for proper conduct of the analgesic measurements. Why then is the lower dose of zomepirac separated from placebo? The following points deserve consideration:

*Demographic distortion.* The standard demographic measures showed no differences between the treatment groups. Both zomepirac treatment groups showed significant differences for operation time, but were not statistically different from each other. More importantly, there was no difference between the trial groups in the proportion of patients with initially severe or moderate pain.

*Inappropriate model.* The chosen model is *a priori* representative of the common situation of musculo-skeletal trauma. The spectrum of pain provides a realistic test for analgesic assessment. The same model has shown previously adequate discrimination and sensitivity (Bullingham et al., 1981; Porter et al., 1981).

*Incorrect assignment of zomepirac doses.* Reexamination of the procedure for packing the tablets showed that confusion in preparing the medications was very unlikely. Quality control check of some of the medications by analysis found the correct zomepirac doses in the correct containers.

*Statistical considerations.* The three active treatment groups could not be differentiated statistically in terms of analgesic effect. A number of comparisons of these same two doses of zomepirac have been made in other trials at other centres, and none has demonstrated zomepirac 100 mg to be significantly better than zomepirac 50 mg (deAndrade et al., 1980; Baird and Turek, 1980; Cooper, 1980a, b; Mayer and Ruoff, 1980; Mehlisch et al., 1980; Messer, Vaughan and Harbert, 1980; Stambaugh, Tejada and Trudnowski, 1980; Wallenstein et al., 1980). This was true for both single and multi-dose studies in a variety of pain models. Zomepirac 100 mg has only been shown to be significantly superior to 50 mg, and then only for analgesic acceptability, in a multidose study in muscle contraction headache (Diamond, 1980). In addition, Forrest (1980) was not able to demonstrate any significant difference between zomepirac 100 mg and 200 mg in patients after operation. Even though the trend of all these results is that zomepirac 100 mg provides more analgesia than does 50 mg, the differences are slight.

One interpretation of these results is that the mean dose–response curve for zomepirac is flat. There will then be little statistical difference between doses as assessed by averaging the results for separate groups of patients. Under these circumstances, it will be difficult to achieve statistical distinction of response between the doses with relatively small numbers of patients, as indeed the quoted literature shows. Furthermore, repeating the comparison of 50 and 100 mg of zomepirac will have a reasonable probability of separating the doses in an unanticipated direction. This is the likely explanation for the results of this trial.

The biological basis for a flat dose–response curve could involve two distinct mechanisms:

(1) The dose–response curve for every individual patient is flat. If this were so, it would be expected that averaging a number of such curves from different individuals would still produce a gently rising dose–response curve. This is incompatible with the clinical observation of a notably fast onset of analgesia with zomepirac and its analgesic equivalence to the usual doses of morphine.

(2) The dose–response curve for an individual is very steep, and with a narrow dose interval between the sharp onset and the plateau. Marked analgesia then occurs at a critical dose, which is different in each individual. Averaging a number of such curves will produce a mean dose–response curve which has a plateau with a gentle rise. This explanation is compatible with a fast onset of analgesia in the individual and with an average equivalence to morphine 10 mg. Furthermore, the class of anti-prostaglandin analgesics is well known to show a limitation of effect beyond a certain dose. The mechanism of action of zomepirac falls within the anti-prostaglandin class (Pruss et al., 1980), so a plateau of effect should appear with zomepirac at some dose. Our results suggest that a high proportion of patients given zomepirac 50 mg have ascended the steep part of their dose–response curve and are already on the plateau. This proposed mechanism could be confirmed by repeated dose–response studies within an individual (including some doses less than 50 mg), or, more efficiently, by plasma concentration–response data.

The practical therapeutic consequences of a flat dose–response curve depend on the clinical context. In the management of acute pain, the therapeutic aim is to control pain as quickly as possible in as many patients as possible; the *first* dose should be the final dose as far as pain relief is concerned. In treatment of acute pain side-effects of the analgesic are often masked by side-effects of the disease or of other drugs. This contrasts with chronic pain, with which the pain will persist and the side-effects of drugs may be especially prominent with prolonged use in an ambulant patient who expects to lead a normal existence. The therapeutic aim here is to define exactly, within the individual, the minimum effective dose.

The strategy, then, for zomepirac in acute pain would be to give at least 100 mg initially; there is even a case for 200 mg. Each higher dose, over a large number of patients, will recruit a few more into the category of initially satisfactory analgesia. Side-effects in acute use with zomepirac are few—there is no difference between 50 mg, 100 mg and placebo in the present study, or 100 mg and 200 mg (Forrest, 1980). In chronic pain, some patients may respond to 50 mg and therefore this could be considered as a starting dose.

Cosalgesic and zomepirac 50 mg both showed a highly significant improvement in mood. The visual analogue scale for mood is not a sophisticated tool, and probably reflects both analgesia and emotional change. The improvement for Cosalgesic may accentuate the latter component, because the patients rated it significantly best on the global assessment. The improvement for zomepirac 50 mg may rather reflect analgesia as suggested by the significantly best global rating by the nurse observer. The nurse observer is most influenced by her analgesic assessments; the patient is more aware of overall improvement including side-effects and mental change. The suspicion must arise that dextropropoxyphene is responsible for the difference in patient global rating.

Zomepirac emerges from this trial as being at least equivalent therapeutically to the dextropropoxyphene/paracetamol mixture. It avoids the problems inherent in any combination (Bullingham et al., 1981) and, importantly, the problems of this particular combination (Young and Lawson, 1980).

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## REFERENCES

deAndrade, R. J., Honig, S., Ciccione, W. J., and Leffall, L. (1980). Clinical comparison of zomepirac with pentazocine in the treatment of postoperative pain. *J. Clin. Pharmacol.*, **20**, 292.

Baird, W. M., and Turek, D. (1980). Comparison of zomepirac sodium, two APC with codeine and placebo in the treatment of moderate and severe postoperative pain. *J. Clin. Pharmacol.*, 20, 243.

Bullingham, R. E. S., McQuay, H. J., Moore, R. A., and Weir, L. (1981). An oral buprenorphine and paracetamol combination compared with paracetamol alone: a single dose double-blind postoperative study. *Br. J. Clin. Pharmacol.*, 12, 863.

Cooper, S. A. (1980a). Efficacy of zomepirac in oral surgical pain. *J. Clin. Pharmacol.*, 20, 230.

—— (1980b). Double-blind comparison of zomepirac sodium, propoxyphene/acetaminophen and placebo in the treatment of oral surgical pain. *Curr. Ther. Res.*, 28, 630.

Diamond, S. (1980). Zomepirac in the symptomatic treatment of muscle contraction headache. *J. Clin. Pharmacol.*, 20, 298.

Forrest, W. H. (1980). Orally administered zomepirac and parenterally administered morphine. *J.A.M.A.*, 244, 2298.

Lasagna, L. (1980). Analgesic methodology: a brief history and commentary. *J. Clin. Pharmacol.*, 20, 373.

Mayer, T. G., and Ruoff, G. E. (1980). Clinical evaluation of zomepirac in the treatment of acute orthopaedic pain. *J. Clin. Pharmacol.*, 20, 285.

Mehlisch, D. R., Joy, E. D., Moore, T. E., Porter, K., Stumpf, A. J., and Wolfe, S. H. (1980). Clinical comparisons of zomepirac with APC/codeine combination in the treatment of pain following oral surgery. *J. Clin. Pharmacol.*, 20, 271.

Messer, R. H., Vaughan, T., and Harbert, G. (1980). Clinical evaluation of zomepirac and APC with codeine in the treatment of postpartum episiotomy pain. *J. Clin. Pharmacol.*, 20, 279.

Porter, E. J. B., Rolfe, M., McQuay, H. J., Moore, R. A., and Bullingham, R. E. S. (1981). Single dose comparison of bicifadine, codeine and placebo in postoperative pain. *Curr. Ther. Res.*, 30, 156.

Pruss, T. P., Gardocki, J. F., Taylor, R. J., and Muschek, L. D. (1980). Evaluation of the analgesic properties of zomepirac. *J. Clin. Pharmacol.*, 20, 216.

Stambaugh, J. E., Tejada, F., and Trudnowski, R. J. (1980). Double-blind comparisons of zomepirac and oxycodone with APC in cancer. *J. Clin. Pharmacol.*, 20, 261.

Wallenstein, S. L., and Houde, R. W. (1975). The clinical evaluation of analgesic effectiveness; in *Methods in Narcotics Research* (eds S. Ehrenpreis and A. Neidle), p. 127. New York: Marcel Dekker.

—— Rogers, A., Kaiko, R. F., Heidrich, G., and Houde, R. W. (1980). Relative analgesic potency of oral zomepirac and intramuscular morphine in cancer patients with postoperative pain. *J. Clin. Pharmacol.*, 20, 250.

Young, R. J., and Lawson, A. A. H. (1980). Distalgesic poisoning—cause for concern. *Br. Med. J.*, 2, 1045.

## COMPARAISON DU ZOMEPIRAQUE, D'UN PLACEBO ET DE L'ASSOCIATION PARACETAMOL–DEXTROPROPOXYPHENE DANS LA DOULEUR POST-OPERATOIRE EN CHIRURGIE ORTHOPEDIQUE

### RESUME

Le zomepiraque sodique a été étudié à deux posologies (50 ou 100 mg) et comparé à une association dextroproxyphène–paracétamol et à un placébo dans un essai randomisé en double-aveugle. Cent vingt patients, ayant une douleur modérée ou sévère après une chirurgie orthopédique mineure, ont été étudiés. Le zomepiraque, à la dose de 50 mg, avait un effet analgésique constamment significatif par rapport au placébo. Le niveau d'analgésie n'était significativement différent que comparé au placébo, pour ce qui est de l'allègement de la douleur et de l'estimation globale de l'observateur. Le zomepiraque, à la dose de 100 mg, n'était pas différent de façon statistiquement significative par rapport au placébo, quelle que soit la mesure de l'analgésie. Le zomepiraque, à la dose de 50 mg, s'est montré au moins équivalent sur le plan thérapeutique à l'association dextropropoxyphrène–paracétamol et pourrait avoir une toxicité moindre.

## ZOMEPIRAC, PLAZEBO UND PARACETAMOL/ DEXTROPROPOXYPHENE KOMBINATION VERGLICHEN BEIM POSTOPERATIVEN SCHMERZ IN ORTHOPÄDISCHEN FÄLLEN

### ZUSAMMENFASSUNG

Zomepirac Sodium, verabreicht in zwei Dosierungen (50 oder 100 mg) wurde mit Dextropropoxyphene/Paracetamol Kombination und Plazebo in einer Doppelblind randomisierten Studie verglichen. Untersucht wurden nach kleineren orthopädische Eingriffen 120 Patienten mit geringen bis schweren Schmerzen. Zomepirac in der Dosierung von 50 mg zeigte im Vergleich zum Plazebo immer den wirksamsten analgetische Effekt. Das übliche Schmerzmittel unterschied sich deutlich vom Plazebo, allerdings nur bezüglich der Schmerzlinderung. Bei der Beurteilung des Schmerzes zeigten 100 mg Zomepirac keinen erheblichen Unterschied zum Plazebo. Zomepirac 50 mg war in seiner Wirksamkeit gleich mit der Kombination Dextropropoxyphene/ Paracetamol und könnte bezüglich der Toxizität Vorteile bieten.

## COMPARACION DE ZOMEPIRAC, DE UN PLACEBO Y DE UNA COMBINACION DE PARACETAMOL Y DEXTROPROPOXIFENO EN RELACION AL DOLOR POSTOPERATIVO PROVOCADO POR INTERVENCIONES QUIRURJICAS DE CARACTER ORTOPEDICO

### SUMARIO

Se analizaron dos dosis (de 50 mg y de 100 mg) de Zomepirac de sodio en contraposición a un placebo y a una combinación de paracetamol y de dextropropoxifeno en un ensayo aleatorio de doble anonimato. Se estudiaron ciento veinto pacientes que sufrían dolor después de la intervención quirúrjica menor de carácter ortopédico, dolor que oscilaba entre el grado moderado y el agudo. La dosis de 50 mg de Zomepirac mostró consistentemente un efecto analgésico significativo en comparación con el placebo. El analgésico típico fue significativamente diferente del placebo tan sólo en lo tocante al alivio del dolor y a la evaluación observador. La dosis de 100 mg de Zomepirac no mostró diferencia estadística significativa con relación al placebo en ninguna de las mediciones analgésicas. La dosis de 50 mg de Zomepirac mostró ser, por lo menos, de una equivalencia terapéutica a la combinación de paracetamol y dextropropoxifeno y puede que presente ventajas en lo tocante a la toxicidad.

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# FREQUENCY OF PAIN ON INJECTION AND VENOUS SEQUELAE FOLLOWING THE I.V. ADMINISTRATION OF CERTAIN ANAESTHETICS AND SEDATIVES

P. KAWAR AND J. W. DUNDEE

## SUMMARY

The frequency of pain on injection and the occurrence of venous sequelae were assessed following the i.v. administration of certain anaesthetic and sedative drugs. Pain on injection occurred frequently following injection in the small veins of the forearm or hand. Pain on injection was greatest with diazepam in organic solvent (Valium) (37%), infrequent with midazolam (1%) and not elicited with diazepam in soya bean oil (Diazemuls). About one in 10 patients complained of pain following thiopentone or methohexitone. There was a 40% frequency of venous thrombosis, assessed on the 7–10th days after Valium. This was virtually absent with Diazemuls and midazolam. A 10% frequency was found following 1% methohexitone and disoprofol (ICI 35 868). We suggest that the injection of Valium should be avoided except in large antecubital veins, although even here the complication rate is higher than with Diazemuls.

Pain on injection is an aspect of the use of i.v. anaesthetic agents of which the anaesthetist may be unaware or may ignore. However, from the patient's point of view, it is of relevance, particularly since the small veins around the wrist or on the back of the hand are used frequently. Thrombosis and thrombophlebitis are other complications of which the patient may be more aware than the anaesthetist. Indeed, in many instances thrombosis does not develop until the 10th or 12th day after administration and may be missed by the anaethetist.

Many reports have been published of the frequency of such sequelae with different i.v. anaesthetics. However, many of these studies have included one or two drugs only, while in others, the variations in methodology have been such as to invalidate any comparison between the different studies. Furthermore, in many of the reported investigations, the period of observation has been limited to the 2–3 days following administration, whereas there is good evidence to show (Hegarty and Dundee, 1977) that the period of observation should be extended to 7–10 days to assess the total frequency of sequelae. Other factors which have not always been standardized include the injection of drugs other than those being studied in the same vein and the use of rapidly running infusions into which the test drug is injected (Graham, Pagano and Conner, 1978). In addition, the method of determining the frequency of sequelae has varied from direct questioning and examination of the patient (Carson et al., 1972; Hegarty and Dundee, 1977; Zacharias et al., 1979; Kortilla and Aromaa, 1980) to the use of questionnaires (Siebke, Ellertsen and Lind, 1976; Mikkelsen, et al., 1980; Olesen and Hüttel, 1980).

In the case of pain on injection, the site of administration and the size of the vein has not always been noted, nor has the nature of the preanaesthetic medication. It would seem reasonable that appropriate premedication may make patients less aware of pain on injection although this has not been borne out in clinical practice (Briggs et al., 1982).

The present paper reports a comprehensive study of pain on injection and venous sequelae following some i.v. anaesthetics and sedatives. These consisted of two commonly used barbiturates, thiopentone and methohexitone, the new i.v. agent ICI 35 868 (disoprofol: di-isopropyl phenol in cremophor), two preparations of diazepam—Valium (organic solvent) and Diazemuls (emulsion)—and the water-soluble benzodiazepine midazolam (table I). A control group of patients was given comparable volumes of normal saline.

## PATIENTS AND METHODS

Apart from those given thiopentone and methohex-

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itone, most of the patients were participating in other studies of induction agents or sedative drugs and were scheduled to undergo either general anaesthesia, a dental procedure or an endoscopic examination. There was no deliberate selection of patients apart from inclusion in the various studies. Thiopentone and methohexitone were given in random order. Saline was given to patients having general anaesthesia who had agreed to this procedure.

Our previous experience with disoprofol had made it ethically unacceptable to inject this into veins on the back of hand or wrist. Apart from this exclusion there was no choice as to the size or site of vein used for injection.

Where the study was limited to the occurrence of pain at the site of injection the patient was asked, before losing consciousness, if there was any discomfort and this was noted; anaesthesia was then continued by any suitable technique. Although the severity of the pain was noted at the time, all degrees of pain, whether elicited on questioning, or as a spontaneous complaint, were eventually pooled.

In the studies relating to the frequency of venous sequelae the injection was limited to a single dose, the needle was withdrawn immediately following injection and a sterile swab applied to the injection site exactly as described by Hewitt and colleagues (1966) and O'Donnell, Hewitt and Dundee (1969). No further injections were made into the same vein and neither measurements of arterial pressure obtained from, nor i.v. infusions sited in that arm, during the rest of the patient's stay in hospital. Difficulties during injection or ecchymosis at the injection site excluded patients from the study.

Patients were seen on the 2nd or 3rd day after operation when they were questioned about discomfort at the site of injection, which was examined, and evidence of pain or thrombosis, or both, noted. Pain was taken to indicate plebitis, whereas thrombosis was recorded if there was hardening of the vein. The length of the thrombosed segment was noted. These latter observations were repeated when the patient was seen, usually at home, on the 7th to 10th days following operation. Although the two series are reported below separately there was some overlap in that, on some occasions both the occurrence of pain on injection and evidence of venous sequelae were assessed in the same patients.

## RESULTS

The drugs studied, their concentrations and solvents and the number of patients in each series, are presented in table I.

### *Pain on injection*

The frequency of reports by the patients of pain on injection is noted in table II. Clearly, the Valium brand of diazepam was the worst in this respect and this complication was eliminated completely when the emulsion (Diazemuls) was used. Pain on injection was very uncommon with midazolam (water-soluble). The frequencies with 2.5% thiopentone and 1.0% methohexitone were similar, being significantly less than the frequency with Valium ($P < 0.001$) although greater than that with disoprofol ($P < 0.05$).

Table III relates the occurrence of pain on injec-

TABLE I. *Drugs studied and numbers of patients*

| Drug | Main solvent | Study: Injection pain | Study: Venous sequelae |
|---|---|---|---|
| 0.9% Saline | Water | 50 | 50 |
| 2.5% Thiopentone | Water | 100 | 50 |
| 1.0% Methohexitone | Water | 100 | 50 |
| 1.0% ICI 35 868 | Cremophor EL | 50 | 50 |
| 0.5% Diazepam | | | |
| Valium | Propylene-glycol | 100 | 50 |
| Diazemuls | Soya bean oil | 50 | 50 |
| 0.5% Midazolam | Water | 400 | 100 |

TABLE II. *Percentage frequency of pain on injection*

| | |
|---|---|
| Saline | 0 |
| Thiopentone | 9 |
| Methohexitone | 12 |
| ICI 35 868 | 4 |
| Diazepam | |
| Valium | 37 |
| Diazemuls | 0 |
| Midazolam | 1 |

TABLE III. *Relationship of pain on injection and the site and size of the vein in three series, each of 100 patients*

| | Size: Large | Size: Others | Site: Antecubital fossa | Site: Others |
|---|---|---|---|---|
| Thiopentone | 1/32 | 8/68 | 0/24 | 9/76 |
| Methohexitone | 3/48 | 9/52 | 5/66 | 7/34 |
| Valium | 3/45 | 34/55 | 4/51 | 33/49 |

TABLE IV. *The frequency of venous sequelae occurring on the 2nd–3rd and 7th–10th days after the administration of various sedatives, anaesthetics and physiological saline*

| | | | | | | Diazepam | | |
|---|---|---|---|---|---|---|---|---|
| Type | Days | Saline | Thiopentone | Methohexitone | ICI 35 868 | Valium | Diazemuls | Midazolam |
| Phlebitis | 2–3 | 1 | 1 | 5 | 4 | 6 | 1 | 2 |
| | 7–10 | 0 | 0 | 3 | 1 | 2 | 0 | 0 |
| Thrombosis | 2–3 | 0 | 0 | 0 | 0 | 3 | 0 | 0 |
| | 7–10 | 0 | 0 | 2 | 0 | 14 | 0 | 3 |
| Thrombophlebitis | 2–3 | 0 | 1 | 0 | 0 | 2 | 0 | 0 |
| | 7–10 | 0 | 0 | 0 | 0 | 2 | 0 | 3 |

tion with three of the drugs to the size and site of the vein. This shows that the greatest frequency of pain occurs in relation to medium or small-sized veins. Likewise, the use of wrist or hand veins for injections produced a greater-frequency than when antecubital veins were used. These differences were highly significant with Valium ($\chi^2 = 32.29$, $P < 0.0001$ for size of vein; $\chi^2 = 37.96$, $P < 0.001$ for site of vein), but not quite so with the others ($0.20 > P > 0.10$).

### *Venous sequelae*

The type, and time of occurrence, of venous sequelae with all the agents studied are detailed in table IV, while table V gives the overall frequency. Valium caused a greater frequency of any complication than methohexitone, ICI 35 868 or midazolam ($P < 0.0005$) and although the frequency with the last three was greater than with saline, thiopentone and Diazemuls, the difference did not reach statistical significance. It would appear that the frequency of "delayed" thrombosis (7–10 days after administration) appeared only to occur with diazepam and midazolam and there was no evidence to suggest that delayed sequelae occurred with either i.v. barbiturate (table IV).

TABLE V. *Overall frequency (%) of all types of sequele in the series referred to in table IV*

| | Days | | |
|---|---|---|---|
| Agent | 2–3 | 7–10 | Total |
| Saline | 2 | 0 | 2 |
| Thiopentone | 4 | 0 | 4 |
| Methohexitone | 10 | 10 | 10 |
| ICI 35 868 | 8 | 2 | 10 |
| Diazepam | | | |
| Valium | 22 | 36 | 40 |
| Diazemuls | 2 | 0 | 2 |
| Midazolam | 2 | 6 | 8 |

TABLE VI. *Venous sequelae related to size of vein*

| | Large vein | | Medium + small veins | |
|---|---|---|---|---|
| Drug | *n* | % | *n* | % |
| 0.9% Saline | 18 | 0 | 32 | 3 |
| 2.5% Thiopentone | 20 | 5 | 30 | 3 |
| 1.0% Methohexitone | 24 | 12 | 26 | 8 |
| 1.0% ICI 35 868 | 24 | 12 | 26 | 8 |
| 0.5% Diazepam | | | | |
| Valium | 28 | 18 | 22 | 32 |
| Diazemuls | 31 | 0 | 19 | 5 |
| 0.5% Midazolam | 65 | 11 | 35 | 3 |

TABLE VII. *Venous sequelae related to site of vein*

| | Site of vein | | | |
|---|---|---|---|---|
| | Antecubital fossa | | Back of hand + wrist | |
| Drug | *n* | % | *n* | % |
| 0.9% Saline | 23 | 0 | 27 | 4 |
| 2.5% Thiopentone | 12 | 17 | 38 | 0 |
| 1.0% Methohexitone | 33 | 12 | 17 | 6 |
| 1.0% ICI 35 868 | 48 | 8 | 2 | 50 |
| 0.5% Diazepam | | | | |
| Valium | 30 | 17 | 20 | 50 |
| Diazemuls | 32 | 0 | 18 | 6 |
| 0.5% Midazolam | 70 | 11 | 30 | 0 |

Table VI relates the frequency of venous sequelae to the size of the vein while a similar analysis for the site of the vein appears in table VII. These two tables should be looked at together because, generally speaking, all small veins were found in sites other than the antecubital fossa. With Valium brand of diazepam the frequency was significantly greater with medium and small veins $P < 0.05$) and when the drug was administered in the back of the hand or the wrist. A surprising find was a greater frequency of thrombosis following the administration of thiopentone and methohexitone in the antecubital fossa than at other sites. However, too firm conclusions must not be drawn from these findings as they only represent a total of seven instances of thrombosis in a series of 100 patients given the two drugs. Likewise, similar findings with midazolam only represent a total of eight instances of thrombosis in 100 administrations.

## DISCUSSION

Those involved in this study were all experienced anaethetists and difficulty in venepuncture or ecchymosis excluded a patient from consideration. It can be firmly stated that the occurrence of both pain on injection and venous thrombosis are related to the drugs used, particularly as there were virtually no complications following the injection of saline.

The frequency of pain following 1% methohexitone and 2.5% thiopentone is surprisingly high and does not appear to have been commented on previously. Despite its widespread use, the severe pain following Valium has rarely been mentioned in the literature. The frequency in this study (37%) is less than the 50% severe and 50% moderate reported by Bahar and co-workers (1982), but the latter workers deliberately used small veins. In the light of these findings (table III) one would recommend that direct i.v. injection of Valium should be into larger antecubital veins. From the clinician's point of view it is gratifying to note that the change of solvent in Diazemuls has abolished this complication completely, while it occurs very infrequently with the water soluble midazolam.

Since there has been no comparable study of the frequency of venous thrombosis there is no advantage in discussing all the publications on this subject. It is sufficient to state that this occurs more frequently than one would have expected and that Valium is the worst offender. The frequency of 40% reported here is almost identical with the 37% reported by Hegarty and Dundee (1977) and much greater than with any other drug in this study. Again the change of solvent in Diazemuls has decreased the frequency with diazepam and it is not a serious problem with midazolam.

If the above recommendation to restrict the direct injection of Valium into large antecubital veins is taken seriously then the frequency of venous thrombosis would be decreased to less than 20%. However, not even this recommendation would make it as acceptable as Diazemuls or midazolam from this particular point of view.

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## REFERENCES

Bahar, M., McAteer, E., Dundee, J. W., and Briggs, L. P. (1982). Aspirin in the prevention of painful intravenous injection of ICI 35 868 and diazepam (Valium). *Anaesthesia*, 37, (in press).

Briggs, L. P., Bahar, M., Beers, H. T. B., Clarke, R. S. J., Dundee, J. W., Wright, P. J., McAuley, D. M., and O'Neill, M. P. (1982). The effect of preanaesthetic medication on anaesthesia with ICI 35 868. *Br. J. Anaesth.*, 54, 303.

Carson, I. W., Alexander, J. P., Hewitt, J. C., and Dundee, J. W. (1972). Clinical studies of induction agents. XLI: Venous sequelae following the use of the steroid anaesthetic agent, Althesin. *Br. J. Anaesth.*, 44, 1311.

Graham, C. W., Pagano, R. R., and Conner, J. T. (1978). Pain and clinical thrombophlebitis following intravenvous diazepam and lorazepam. *Anaesthesia*, 33, 188.

Hegarty, J. E., and Dundee, J. W. (1977). Sequelae after the intravenous injection of three benzodiazepines—diazepam, lorazepam and flunitrazepam. *Br. Med. J.*, 2, 1384.

Hewitt, J. C., Hamilton, R. C., O'Donnell, J. F., and Dundee, J. W. (1966). Clinical studies of induction agents. XIV: A comparative study of venous complications following thiopentone, methohexitone and propanidid. *Br. J. Anaesth.*, 38, 115.

Kortilla, A., and Aromaa, U. (1980). Venous complications after intravenous injection of diazepam, flunitrazepam, thiopentone and etomidate. *Acta Anaesthesiol. Scand.*, 24, 227.

Mikkelsen, H., Hoel, T. M., Bryne, H., and Krohn, C. D. (1980). Local reactions after intravenous injections of diazepam, flunitrazepam and isotonic saline. *Br. J. Anaesth.* 52, 817.

O'Donnell J. F., Hewitt, J. C., and Dundee, J. W. (1969). Clinical studies of induction agents. XXVIII: A further comparison of venous complications following thiopentone, methohexitone and propanidid. *Br. J. Anaesth.*, 41, 681.

Olesen, A. S., and Hüttel, M. S. (1980). Local reactions to intravenous diazepam in three different formulations. *Br. J. Anaesth.*, 52, 609.

Siebke, H., Ellertsen, B. B., and Lind, B. (1976). Reactions to intravenous injections of diazepam. *Br. J. Anaesth.*, 48, 1187.

Von Dardel, O., Mebius, C., and Mossberg, T. (1976). Diazepam in emulsion form for intravenous usage. *Acta Anaesthesiol. Scand.*, 20, 221.

Zacharias, M., Clarke, R. S. J., Dundee, J. W., and Johnston, S. B. (1979). Venous sequelae following etomidate. *Br. J. Anaesth.*, 51, 779.

## FREQUENCE DE LA DOULEUR LORS DE L'INJECTION ET DE SEQUELLES VEINEUSES APRES ADMINISTRATION I.V. DE CERTAINS ANESTHESIQUES ET SEDATIFS

### RESUME

La fréquence de douleurs lors de l'injection et de la survenue de séquelles veineuses après administration i.v. de certains agents anesthésiques et sédatifs a été recherchée. La douleur à l'injection était fréquente après injection dans les petites veines de l'avant-bras et de la main. La douleur à l'injection était particulièrement fréquente avec le diazépam dans un solvant organique (Valium, 37%), rare avec le midazolam (1%) et non retrouvée avec le diazépam dans l'huile de soja (Diazemuls). Environ un patient sur dix s'est plaint de douleur à l'injection de thiopentone ou de méthohéxitone. La fréquence des thromboses veineuses était de 40%, quand on les recherchait 7–10 jours après diazépam. Ceci n'existait pratiquement pas avec le Diazemuls et le midazolam. Une fréquence de 10% a été retrouvée après le méthohexitone 1% et le disoprofol (ICI 35 868). Nous conseillons d'éviter les injections de diazépam, sauf dans des grosses veines de l'avant-bras, bien que même dans ce cas la fréquence des complications soit plus importante qu'avec le Diazemuls.

## DIE HÄUFIGKEIT VON SCHMERZ UND SCHÄDIGUNGEN DER VENEN NACH I.V. GABE VON BESTIMMTEN ANÄSTHETIKA UND SEDATIVA

### ZUSAMMENFASSUNG

Es wurde die Häufigkeit von Schmerzen und Beschwerden in den Venen nach i.v. Gabe von bestimmten Anästhetika und Sedativa untersucht. Ein Injektionsschmerz trat häufig nach Injektion in die kleinen Venen am Unterarm oder der Hand auf. Der Injektionsschmerz war am größten bei Diazepam in organischem Lösungsmittel (37%), selten bei Midazolam (1%) und fehlte ganz bei Diazepam in Soyabohnenöl (Diazemuls). Ungefähr einer unter 10 Patienten klagte über Schmerz nach Thiopental oder Methohexital. Die Häufigkeit von venösen Thrombosen nach Diazepam betrug 40%, bei Untersuchung am sieben bis 10. Tag nach Diazepamgabe. Dies trat bei Diazemuls und Midazolam gar nicht auf. Eine Häufigkeit von 10% wurde nach Methohexital 1% und nach Disoprofol gefunden (ICI 35 868). Wir schlagen vor, die Injektion von Diazepam zu vermeiden, außer Kubitalvenen, abwohl sogar hier die Komplikationsrate größer ist als bei Diazemuls.

## FRECUENCIA DE DOLOR DURANTE LA INYECCION Y MARCAS VENOSAS A RAIZ DE LA ADMINISTRACION INTRAVENOSA DE CIERTOS SEDATIVOS Y SUBSTANCIAS ANESTESICAS

### SUMARIO

Se evaluó la frecuencia del dolor durante la inyección y la aparición de secuelas venosas a raiz de la administración intravenosa de ciertos anestésicos y drogas sedativas. Con frecuencia apareció dolor durante la inyección a raiz de efectuarse ésta en las pequeñas venas del antebrazo o de la mano. El dolor fue mayor al usar diazepam disuelto en substancias orgánicas (Valium) (37%) y poco frecuente al usar midazolam (1%), no detectándose dolor alguno al usar diazepam disuelto en aceite de soja (Diazemuls). Uno de cada 10 de los pacientes se quejó de dolor a raiz del uso de tiopentona o de metohexitona. Entre el 7° y el 10° día de la administración de diazepam se evaluó la frecuencia de la trombosis venosa, obteniéndose la cifra del 40%. Dicha frecuencia no existió al usar Diazemuls y midazolam. Se encontró una frecuencia del 10% como consecuencia de un 1% de metohexitona y de disoprofol (ICI 35,868). Sugerimos que la inyección de diazepam debe evitarse, a menos que se efectúe en gran venas antecubitales, aunque incluso en esta zona el índice de complicaciones es superior al de Diazemuls.

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# PORCINE MALIGNANT HYPERTHERMIA. VIII: LEG METABOLISM

G. M. HALL, J. N. LUCKE, C. ORCHARD, R. LOVELL AND D. LISTER

SUMMARY

Leg metabolism during porcine malignant hyperthermia (MH) was investigated in eight Pietrain pigs. There was an efflux of glucose, lactate, pyruvate and alanine from the leg during MH, demonstrating the occurrence of rapid glycogen degradation. Potassium production by the leg did not change significantly and the decrease in free fatty acid efflux together with the maintenance of glycerol production suggested the utilization of intramuscular triglycerides. The failure of leg blood flow to increase during MH limited the oxygen consumption of the muscle as maximal oxygen extraction occurred early in the response. In a further six Pietrain pigs it was shown that the infusion of sodium nitroprusside increased leg blood flow only slightly. It is possible that the inability of leg blood flow to increase in MH was a result of the decline in cardiac output.

There is surprisingly little information on the contribution of the increase in muscle metabolism during porcine malignant hyperthermia (MH) to the changes observed in circulating metabolites. It is, moreover, not possible to infer the contribution of skeletal muscle by studying changes in central venous metabolite values because of the important and variable effects of hepatic metabolism during MH (Hall et al., 1980). Therefore, in the present study we have systematically examined hind leg metabolism during MH and we have been obliged to use femoral arterial and venous blood samples. A single muscle preparation, such as gracilis in the dog, could not be developed in the pig because of the extremely small size of the peripheral blood vessels and the compact morphology of the leg muscles. A similar technique was used by Gronert and colleagues (Gronert, Milde and Theye, 1976a, b; Gronert and Theye, 1976) to quantify the increased muscle metabolism in MH, but the only substrates measured were lactate and pyruvate.

The results of the first experiment in the present studies showed that leg blood flow failed to increase to match the marked stimulation of muscle metabolism. Since Williams and colleagues have argued consistently that catecholamine-mediated vasoconstriction is a major factor in the pathogenesis of porcine MH (Williams, Hoech and Roberts, 1978; Williams et al., 1978), we undertook a second experiment to examine the effect of sodium nitroprusside (SNP) on leg blood flow and metabolism during MH.

## METHODS

Eight Pietrain pigs (mean weight 60 kg, SEM ± 2 kg) from the Meat Research Institute's herd were studied. Anaesthesia was induced by an injection of thiopentone 10–15 mg kg$^{-1}$ through an ear vein. After intubation of the trachea, the lungs were ventilated with 66% nitrous oxide in oxygen using a Cape–Waine ventilator, and anaesthesia was maintained with incremental doses of thiopentone. Twenty-gauge Teflon cannulae, 3 cm long, were placed in both femoral arteries and veins approximately 1 cm distal to the femoral ring and the patency of the cannulae maintained by intermittent flushing with a 0.9% sodium chloride solution. A thermocouple was placed 10 cm deep into the biceps femoris muscle for measurement of muscle temperature.

Approximately 45 min after the induction of anaesthesia control femoral arterial and venous blood samples were collected simultaneously for the measurement of pH, oxygen content, glucose, lactate, pyruvate, alanine, free fatty acids (FFA), glycerol and potassium by methods described in detail previously (Hall et al., 1980). In addition, the

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haematocrit and the adenosine concentration (Möllering and Bergmeyer, 1974) of the arterial sample were determined. Leg blood flow was estimated by the infusion of the dye indocyanine green into the femoral artery according to the method of Jorfeldt and Wahren (1971), but with a decreased dye concentration of 200 $\mu$g ml$^{-1}$. Arterial pressure was measured as described by Lucke, Hall and Lister (1976). MH was then induced by ventilating the lungs with 1% halothane for 10 min and the administration of suxamethonium 1 mg kg$^{-1}$ after 5 min ventilation with halothane. Paired femoral arterial and venous samples were collected every 10 min until the pig died.

*Sodium nitroprusside infusion*

Six Pietrain pigs (mean weight 60 kg, SEM ± 3 kg) were prepared as described above. After control samples were collected, SNP was infused in 0.9% sodium chloride solution to decrease the mean arterial pressure (m.a.p.) to approximately half the control value for 15 min, when a second group of measurements were made. MH was then induced as described previously and paired femoral arterial and venous samples collected every 10 min. In this experiment the measurement of circulating metabolites was confined to lactate, glucose and potassium. The rate of SNP infusion was varied during the hyperthermic response to maintain the m.a.p. at the lower value (mean total dose 36 mg, SEM ± 4 mg).

The results are presented as mean values (± SEM). The significance of a change in mean values with time in each experiment was assessed by a two-way analysis of variance. Student's *t* test for unpaired data was used to determine the presence of a significant difference in mean values between the two experiments.

## RESULTS

*Leg blood flow* (table I)

Leg blood flow increased slightly from 0.40 litre min$^{-1}$ to 0.47 litre min$^{-1}$ after 10 min of MH, but then decreased during the remainder of the hyperthermic response to 0.25 litre min$^{-1}$ terminally ($P < 0.05$). Arterial oxygen content did not change during MH but the arterio–femoral venous difference in oxygen content ($Ca_{O_2} - Cv_{O_2}$) increased significantly ($P < 0.001$) after 10 min. The increased oxygen extraction enabled oxygen uptake by the leg to increase significantly ($P < 0.05$) after 10 min from 24 to 69 ml min$^{-1}$, but this was not maintained because of the progressive decline in leg blood flow. The reduction in arterial pH and increases in haematocrit and muscle temperature, which are characteristic signs of MH, were significantly different from control values after only 10 min ($P < 0.001$, $< 0.001$ and $< 0.01$ respectively). M.a.p. decreased during MH to 69 mm Hg after 30 min ($P < 0.01$).

*Arterial substrate concentrations* (table II)

MH was associated with a progressive hyperglycaemia which reached 13.7 mmol litre ($P < 0.001$) after 40 min. Plasma potassium concentration increased rapidly from 4.3 to 7.3 mmol litre$^{-1}$ ($P < 0.001$) after only 10 min of MH, but there was little further change. Arterial lactate values increased significantly ($P < 0.001$) during MH as did pyruvate concentrations, although more slowly, and became significant ($P < 0.05$) after 30 min. There was almost a three-fold increase in arterial alanine concentration from 80 $\mu$mol litre$^{-1}$ in the control period to 218 $\mu$mol litre$^{-1}$ ($P < 0.001$) after 40 min. Arterial FFA concentrations did not change during MH, whereas a significant increase ($P < 0.01$) in glycerol values was found after only 10 min. The arterial adenosine value increased more than five-fold to 8.4 $\mu$mol litre$^{-1}$ ($P < 0.05$) after 10 min and this increase persisted during MH.

*Leg metabolism* (table III)

The uptake or efflux of metabolites was calculated from the product of the difference between the arterial and femoral venous concentrations of the metabolite and the leg blood flow or plasma flow as appropriate. The limitations of using the Fick principle during MH have been discussed previously (Hall et al., 1980).

There was a small uptake of glucose by the leg in the control period, but after 10 min of halothane a significant release ($P < 0.05$) of 0.55 mmol min$^{-1}$ was observed. Efflux of glucose from the leg occurred until the terminal stages of MH. Throughout the hyperthermic response there was a significant production ($P < 0.01$) of lactate by the leg which was maximal (0.87 mmol min$^{-1}$) after 10 min. Small increases in the efflux of potassium, pyruvate and alanine were found, but this change was significant ($P < 0.05$) only for pyruvate after 10 and 20 min. FFA release by the leg decreased significantly during MH ($P < 0.05$ and $< 0.01$), but glycerol production was maintained.

TABLE I. *Leg blood flow: mean (± SEM) values for leg physiology during MH.* n = *number of pigs studied. Significance of difference of means from control:* *P $< 0.05$, **P $< 0.01$, ***P $< 0.001$

| | *n* | Control | Malignant hyperthermia | | | |
|---|---|---|---|---|---|---|
| | | −10 min | 10 min | 20 min | 30 min | 40 min |
| Arterial pH (units) | 8 | 7.39±0.02 | 7.05± 0.03*** | 6.77± 0.02*** | 6.71± 0.02*** | 6.70±0.03*** |
| Arterial $O_2$ content (ml $dl^{-1}$) | 6 | 16.2 ±0.7 | 15.5 ± 1.3 | 14.1 ± 1.0 | 14.8 ± 1.3 | 14.8 ±1.8 |
| Leg blood flow (litre $min^{-1}$) | 7 | 0.40±0.05 | 0.47± 0.09 | 0.33± 0.05 | 0.27± 0.06 | 0.25±0.05* |
| ($Ca_{O_2} - Cv_{O_2}$) (ml $dl^{-1}$) | 6 | 5.9 ±0.5 | 13.4 ± 18* | 42 ± 7 | 41 ±10 | 36 ±6 |
| Leg $O_2$ uptake (ml $min^{-1}$) | 6 | 24 ±3 | 69 ±18* | 42 ±7 | 41 ±10 | 36 ±6 |
| Haematocrit (%) | 8 | 36.6 ±0.6 | 44.9 ± 0.9*** | 47.8 ± 1.2*** | 48.6 ± 1.1*** | 47.9 ±1.1*** |
| Muscle temperature (°C) | 8 | 38.9 ±0.1 | 39.7 ± 0.2** | 41.1 ± 0.2*** | 42.0 ± 0.3*** | 42.8 ±0.3*** |
| M.a.p. (mm Hg) | 7 | 101 ±8 | 82 ±13 | 76 ±10* | 69 ±11** | — |

TABLE II. *Mean (±SEM) arterial concentrations of metabolites during MH.* n = *number of pigs studied. Significance of difference of means from control:* *P $< 0.05$, **P $< 0.01$, ***P $< 0.001$

| | *n* | Control | Malignant Hyperthermia | | | |
|---|---|---|---|---|---|---|
| | | −10 min | 10 min | 20 min | 30 min | 40 min |
| Glucose (mmol $litre^{-1}$) | 8 | 4.9 ± 0.4 | 5.7 ± 0.6 | 9.5 ± 1.1** | 10.9 ± 1.6** | 13.7 ± 2.3*** |
| Potassium (mmol $litre^{-1}$) | 8 | 4.3 ± 0.1 | 7.3 ± 0.6*** | 7.5 ± 0.4*** | 7.6 ± 0.6*** | 7.6 ± 0.8*** |
| Lactate (mmol $litre^{-1}$) | 8 | 1.1 ± 0.3 | 8.6 ± 0.6*** | 14.9 ± 1.4*** | 17.1 ± 1.3*** | 18.9 ± 1.5*** |
| Pyruvate (μmol $litre^{-1}$) | 6 | 66 ±16 | 94 ±27 | 103 ±21 | 115 ±20* | 111 ±27 |
| Alanine (μmol $litre^{-1}$) | 7 | 80 ±11 | 114 ±10 | 146 ±17** | 179 ± 8*** | 218 ±12*** |
| FFA (mmol $litre^{-1}$) | 8 | 0.23± 0.05 | 0.21± 0.05 | 0.19± 0.05 | 0.15± 0.06 | 0.15± 0.06 |
| Glycerol (mmol $litre^{-1}$) | 8 | 0.17± 0.02 | 0.28± 0.02** | 0.33± 0.02** | 0.31± 0.05* | 0.35± 0.06* |
| Adenosine (μmol $litre^{-1}$) | 6 | 1.5 ± 0.8 | 8.4 ± 3.1* | 4.8 ± 1.4* | 7.9 ± 2.9* | 6.1 ± 3.1 |

TABLE III. *Leg metabolism: mean (±SEM) leg exchange of metabolites during MH. Positive values indicate leg uptake and negative values indicate leg production.* n = *number of pigs studied. Significance of difference of means from control:* *P <0.05, **P <0.01. ***P <0.001

| | | Control | Malignant hyperthermia | | | |
|---|---|---|---|---|---|---|
| | n | −10 min | 10 min | 20 min | 30 min | 40 min |
| Glucose (mmol min⁻¹) | 7 | 0.28±0.15 | − 0.55± 0.25* | − 0.02± 0.11 | − 0.11± 0.15 | 0.35± 0.13 |
| Lactate (mmol min⁻¹) | 7 | 0.10±0.04 | − 0.87± 0.29** | − 0.80± 0.24** | − 0.35± 0.09** | − 0.65± 0.22** |
| Potassium (µmol min⁻¹) | 7 | −18 ±6 | −28 ±17 | −39 ±34 | −90 ±39 | −39 ±25 |
| Pyruvate (µmol min⁻¹) | 5 | 0 ±2 | − 8 ± 2** | − 6 ± 2* | − 3 ± 2 | − 3 ± 2 |
| Alanine (µmol min⁻¹) | 6 | − 3 ±2 | −14 ± 6 | − 8 ± 4 | − 7 ± 1 | − 6 ± 2 |
| FFA (µmol min⁻¹) | 7 | −16 ±4 | − 1 ± 4* | − 2 ± 2** | 2 ± 2** | 3 ± 2** |
| Glycerol (µmol/min⁻¹) | 7 | − 9 ±3 | − 4 ± 4 | − 4 ± 4 | − 5 ± 3 | − 4 ± 6 |

TABLE IV. *Mean (±SEM) leg physiology and metabolism during MH with sodium nitroprusside infusion.* n = *number of pigs studied. Significance of difference of means from control:* *P< 0.05, **P< 0.01, ***P< 0.001

| | | Control | SNP | Malignant hyperthermia | | |
|---|---|---|---|---|---|---|
| | n | −20 min | −5 min | 10 min | 20 min | 30 min |
| Arterial pH | 6 | 7.41±0.02 | 7.46±0.03 | 7.04± 0.06*** | 6.82± 0.05*** | 6.72± 0.03*** |
| Arterial $O_2$ content (ml dl⁻¹) | 6 | 14.7 ±1.1 | 13.9 ±0.09 | 12.4 ± 1.8 | 12.1 ± 1.3 | 12.3 ± 1.1 |
| Leg blood flow (litre min⁻¹) | 6 | 0.39±0.07 | 0.19±0.02** | 0.54± 0.09 | 0.58± 0.17 | 0.45± 0.10 |
| Leg $O_2$ uptake (ml min⁻¹) | 6 | 20 ±4 | 16 ±1 | 58 ±15 | 62 ±23 | 49 ±12 |
| Haematocrit (%) | 6 | 32.3 ±1.7 | 32.3 ±2.0 | 39.7 ± 2.0*** | 41.5 ± 2.6*** | 42.3 ± 2.8*** |
| Muscle temperature (°C) | 6 | 38.4 ±0.3 | 38.2 ±0.2 | 39.0 ± 0.2* | 40.1 ± 0.5** | 41.0 ± 0.6*** |
| M.a.p. (mm Hg) | 6 | 104 ±8 | 56 ±3** | 58 ± 4** | 57 ± 6** | 61 ±5** |
| Arterial lactate (mmol min⁻¹) | 6 | 1.1 ±0.4 | 0.9 ±0.5 | 11.8 ± 1.2*** | 18.4 ± 2.0*** | 19.5 ± 1.9*** |
| Arterial glucose (mmol litre⁻¹) | 6 | 4.7 ±0.2 | 4.9 ±0.2 | 5.9 ± 0.6 | 7.6 ± 0.6** | 8.2 ± 1.2** |
| Arterial potassium (mmol litre⁻¹) | 6 | 4.0 ±0.1 | 4.0 ±0.1 | 6.4 ± 0.6** | 6.6 ± 0.5** | 7.3 ± 0.4*** |

*Sodium nitroprusside infusion* (table IV)

The course of the hyperthermic response was particularly rapid when SNP was administered so that a complete set of data was available for only 30 min of MH.

SNP infusion in the control period produced a decrease in m.a.p. from 104 to 56 mm Hg ($P < 0.01$). Leg blood flow was halved during this time, but oxygen extraction increased so that there was no significant change in oxygen uptake by the leg. The maintenance of SNP during MH was associated with an improvement in leg blood flow compared with the previous experiment, but this failed to reach the level of statistical significance ($P < 0.15$). The metabolic response in MH was not affected by SNP infusion.

The haematocrit was decreased significantly ($P < 0.05$) in the SNP group of pigs compared with the previous experiment and this was reflected by the slightly decreased arterial oxygen contents.

## DISCUSSION

Femoral venous blood drains two metabolically active tissues, muscle and subcutaneous fat. Dissection data show that in Pietrain pigs of 60 kg live weight, the hind leg weighs 5.75 kg, of which 66% is muscle, 18% fat, 11% bone and 5% other tissues (Meat Research Institute's unpublished results). Adipose tissue is known to utilize glucose so that its glucose uptake undoubtedly contributed to the arterio–femoral venous glucose difference observed in the control period. Blood flow to subcutaneous fat during MH has not been determined, but it is likely to decline rapidly with the increase in circulating catecholamines (Lucke, Hall and Lister, 1976). In view of the large muscle mass in the leg and the rapid increase in arterio–femoral venous oxygen content difference, it is a reasonable assumption that the changes observed in substrate exchange primarily represent alterations in muscle metabolism. A similar hypothesis has been demonstrated to be valid during severe exercise in man (Wahren et al., 1971).

The release of free glucose by the leg during MH was a surprising finding, since muscle does not contain the enzyme glucose-6-phosphatase (Manners, 1964). Wahren (1970) also observed the production of glucose by forearm musculature during intense exercise. It is known that about 8% of glycogen appears in the form of free glucose during glycogenolysis, but at normal rates of glycogen degradation this undergoes immediate phosphorylation (Field, 1960). Wahren (1970) suggested that glucose production by muscle arose as the result of extremely rapid glycogenolysis in the presence of increased glucose-6-phosphate concentrations which inhibit hexokinase. This explanation is also tenable in MH as Mitchell, Heffron and van Rensburg (1980) have shown recently that muscle concentrations of glucose-6-phosphate increase during the hyperthermic response. The muscle glycogen degradation occurring in MH was accompanied by the efflux of lactate, pyruvate and alanine from the leg. It is noteworthy that after 20 min of MH the uptake of lactate by the liver (Hall et al., 1980) was just greater than the lactate production of *one* hind leg (table III).

The failure of plasma FFA concentrations to increase during MH was noted previously and considered to be a result of either the inhibition of lipolysis by the lactic acidosis (Lucke, Hall and Lister, 1976) or immediate re-esterification of the fatty acids (Hall et al., 1980). The results of the present study suggest a different explanation as gylcerol production by the leg was maintained in the presence of a significant decrease in FFA release. Thus, triglyceride breakdown continued during MH with local oxidation of the fatty acids. Our results do not allow a definite conclusion to be reached of whether the site of these changes in fat metabolism is adipose tissue or muscle. However, Jones and others (1980) observed similar changes during intense exercise. They concluded that lipolysis in adipose tissue was inhibited at high levels of muscular work and that hydrolysis of intramuscular triglycerides was increased. A direct study of changes in muscle triglyceride values during MH will enable the role of intramuscular lipids as an energy source to be verified.

We have shown previously that that there is a major efflux of potassium from the liver early in the hyperthermic response (Hall et al., 1980). Potassium production by the leg was surprisingly small and reached a maximum of only 90 μmol min$^{-1}$ after 30 min of MH (table III). The results do not support the contention of Gronert (1980) that there is a significant late efflux of potassium from muscle and we conclude that the liver is the main source of hyperkalaemia in MH.

The failure of leg blood flow in MH to match the increase in muscle activity severely limited oxygen consumption by the leg and probably accounted for the early onset of anaerobic metabolism. SNP had only a small beneficial effect on leg blood flow, suggesting that catecholamine-mediated vasoconstriction had little influence on muscle blood flow. It is likely that the main action of SNP was to augment skin blood flow and increase heat loss as shown by the decreased muscle temperatures. Other local factors may have been responsible for the inadequate muscle blood flow. For example, muscle oedema and stiffness occur rapidly in MH (Berman et al., 1970) and may close thin-walled, low-pressure blood vessels. However, the increase in arterial adenosine values found during MH suggests that the release of local vasodilators by muscle occurred normally (Haddy and Scott, 1968).

It is possible that a progressive decline in cardiac output was responsible for the inadequate leg blood flow (Gronert and Theye, 1976). The decrease in cardiac output during MH is not surprising in view of the associated acidosis, hyperkalaemia and haemoconcentration. Some support for the role of the cardiac output as an important determinant of leg flow is afforded by the results of Gronert, Milde and Theye (1976b) which showed an improvement in cardiac output and leg blood flow in MH by the vigourous treatment of the acidosis alone.

In conclusion, the increases in circulating lactate, pyruvate and alanine concentrations found in porcine MH result from extremely rapid muscle glycogenolysis, which also makes a small contribution to the hyperglycaemia. There was no significant potassium efflux by the leg and the changes in FFA and glycerol metabolism probably reflected the oxidation of intramuscular triglycerides. Oxidative metabolism by leg musculature during MH is limited by the inadequate blood flow, probably secondary to the decline in cardiac output.

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REFERENCES

Berman, M. C., Harrison, G. G., Bull, A. B., and Kench, J. E. (1970). Changes underlying halothane-induced malignant hyperpyrexia in Landrace pigs. *Nature (Lond).*, 225, 653.

Field, R. A. (1960). Glycogen deposition diseases; in *The Metabolic Basis of Inherited Disease* (eds J. B. Stanbury, J. B. Wyngarden and D. S. Frederickson), p. 156. New York: McGraw-Hill.

Gronert G. A. (1980). Malignant hyperthermia. *Anesthesiology*, 53, 395.

Gronert, G. A., Milde, J. H., and Theye, R. A. (1976a). Porcine malignant hyperthermia induced by halothane and suxamethonium: failure of treatment with procaine or procainamide. *Anesthesiology*, 44, 124.

——— ——— ——— (1976b). Dantrolene in porcine malignant hyperthermia. *Anesthesiology*, 44, 488.

—— Theye, R. A. (1976). Halothane-induced porcine malignant hyperthermia: metabolic and hemodynamic changes. *Anesthesiology*, 44, 36.

Haddy, F. J., and Scott, J. B. (1968). Metabolically linked vasoactive chemicals in the local regulation of blood flow. *Physiol. Rev.*, 16, 292.

Hall, G. M., Lucke, J. N., Lovell, R., and Lister, D. (1980). Porcine malignant hyperthermia. VII: Hepatic metabolism. *Br. J. Anaesth.*, 52, 11.

Jones, N. L., Heigenhauser, G. J. F., Kuksis, A., Matsos, C. G., Sutton, J. R., and Toews, C. J. (1980). Fat metabolism in heavy exercise. *Clin. Sci.*, 59, 469.

Jorfeldt, L., and Wahren, J., (1971). Leg blood flow during exercise in man. *Clin. Sci.*, 41, 459.

Lucke, J. N., Hall, G. M., and Lister, D. (1976). Porcine malignant hyperthermia. I: Metabolic and physiological changes. *Br. J. Anaesth.*, 48, 297.

Manners, D. J. (1964). Glycogen storage disease, type 1; in *Control of Glycogen Metabolism* (ed. E. J. Whelan), p. 83; Ciba Foundation Symposium. London: Churchill.

Mitchell, G., Heffron, J. J. A., and van Rensburg, A. J. J. (1980). A halothane-induced biochemical defect in muscle of normal and malignant hyperthermia-susceptible Landrace pigs. *Anesth. Analg. (Cleve.)*, 59, 250.

Möllering, H., and Bergmeyer, H. U. (1974). Adenosine; in *Methods of Enzymatic Analysis*, 3rd edn (ed. H. U. Bergmeyer), p. 1919. Berlin: Springer-Verlag.

Wahren, J. (1970). Human forearm muscle metabolism during exercise IV. Glucose uptake at different work intensities. *Scand. J. Clin. Lab. Invest.*, 25, 129.

—— Felig, P., Ahlborg, G., and Jorfeldt, L. (1971). Glucose metabolism during exercise in man. *J. Clin. Invest.*, 50, 2715.

Williams, C. H., Hoech, G. P., and Roberts, J. T. (1978). Experimental malignant hyperthermia. *Anesthesiology*, 49, 58.

—— Shanklin, M. D., Hedrick, H. B., Muhrer, M. E., Stubbs, D. H., Krause, G. F., Payne, C. G., Benedict, J. D., Hutcheson, D. P., and Lasey, J. F. (1978). The fulminant hyperthermia stress syndrome: genetic aspects, hemodynamic and metabolic measurements in susceptible and normal pigs; in *Second International Symposium on Malignant Hyperthermia* (eds J. A. Aldrete, and B. A. Britt), p. 113. New York: Grune and Stratton.

## L'HYPERTHERMIE MALIGNE CHEZ LE PORC. VIII: LE METABOLISME DE LA PATTE

RESUME

Le métabolisme a été étudié au niveau de la patte au cours de l'hyperthermie maligne chez le porc (HM) chez huit porcs Pietrain. Il y avait un efflux de glucose, de lactate, de pyruvate et d'alanine de la patte au cours de l'HM, ce qui apportait la preuve d'une dégradation rapide du glycogène. La production de potassium par la patte n'était pas modifiée de façon significative et la diminution de l'efflux d'acides gras libres, associée à un taux constant de production du glycérol faisait penser à une consommation des triglycérides intramusculaires. Le fait que le débit

sanguin de la patte n'augmentait pas au cours de l'HM limitait la consommation d'oxygène du muscle dans la mesure où l'extraction la plus importante de l'oxygène survenait précocement dans la réponse. Ultérieurement, ches six autres porcs Pietrain, on a montré que la perfusion de nitroprussiate de sodium n'augmentait que légèrement le débit sanguin de la patte. Il est possible que l'incapacité du débit sanguin dans la patte à augmenter dans l'HM soit la conséquence d'une diminution du débit cardiaque.

## DIE MALIGNE HYPERTHERMIE DES SCHWEINES VIII: DER STOFFWECHSEL DES BEINES

### ZUSAMMENFASSUNG

Der Stoffwechsel des Beines während der malignen Hyperthermie (MH) des Schweines wurde bei acht Schweinen untersucht. Ein Ausstrom von Glukose, Laktat, Pyruvat und Alanin aus dem Bein während der MH zeigte, daß ein rapider Glykogenabbau stattfand. Der Kaliumausstrom aus dem Bein änderte sich nicht signifikant, und der Abfall des Ausstromes von freien Fettsäuren zusammen mit weiterbestehender Glyzerolproduktion wies auf den Verbrauch von intramuskulären Triglyzeriden hin. Da eine Erhöhung des Blutflusses zum Bein während der MH nicht zustandekam, war der Sauerstoffverbrauch des Muskels, der am Anfang der Reaktion maximal war, beschränkt. Bei weiteren sechs Schweinen zeigte sich, daß die Infusion von Natriumnitroprussid den Blutstrom zum Bein nur leicht ansteigen ließ. Möglicherweise ist das Nichtansteigen des Blutstromes zum Bein auf einen Abfall des Herzminutenvolumens zurückzuführen.

## HIPERTERMIA MALIGNA EN EL CERDO VIII: METABOLISMO DE LA PATA

### SUMARIO

Se investigó el metabolismo de las patas de 8 cerdos Pietrain aquejados de hipertermia maligna (HM). Hubo un derrame de glucosa, lactatos, piruvatos y alanina en las patas durante la HM, lo que pone de manifiesto la rápida degradación de glicógeno. La producción de potasio en la pata no cambió de forma significativa al tiempo que la disminución en el derrame de ácidos grasos de radical libre, junto con el mantenimiento de la productión de glicerol, sugirió el uso de trigliceridas intramusculares. La falta de aumento en el flujo sanguíneo de la pata durante la HM limitó el consumo de oxígeno por parte del músculo, a medida que tuvo lugar la máxima extracción de éste elemento al principio de la respuesta. En otros seis cerdos Pietrain se mostró que la infusión de nitroprusiato de sodio aumento el riego sanguíneo de la pierna en cantidades muy pequeñas. Es posible que el no poder aumentar el riego sanguíneo durante la HM sea el resultado de una disminución de la produccón cardiaca.

*Br. J. Anaesth.* (1982), 54, 949

# ADENYLATE KINASE AND MALIGNANT HYPERPYREXIA

L. A. MARJANEN AND M. A. DENBOROUGH

## SUMMARY

The isoenzyme pattern and activity of adenylate kinase was studied in muscle and red blood cells from individuals and swine shown to be susceptible to malignant hyperpyrexia. No abnormality in adenylate kinase isoenzyme pattern or activity was found.

Malignant hyperpyrexia (MH) occurs in individuals and swine with an underlying disease of skeletal muscle (Denborough, 1980). The enzyme adenylate kinase (AK), a phosphotransferase, catalyses the reversible reaction: $2\,ADP \rightleftharpoons ATP + AMP$, occurs in many tissues and plays an important role in regulating the concentration of cellular adenine nucleotide (Noda, 1973). During an episode of MH muscle adenosine triphosphate (ATP) is depleted (Harrison et al., 1969). However, although a deficiency of skeletal muscle adenylate kinase was reported in one family susceptible to MH (Schmitt, Schmidt and Ritter, 1974), in another investigation no abnormality was found in skeletal muscle adenylate kinase in MH (Cerri et al., 1981).

As a result of the disparity in these findings investigations were undertaken on adenylate kinase in both red blood cells and skeletal muscle from man and swine susceptible to MH. The findings were compared with those from normal individuals and non-susceptible swine.

## METHODS

### *Susceptibility to MH*

In all instances susceptibility was assessed on muscle biopsy samples by pharmacological methods which have been described previously (Moulds and Denborough, 1974; Okumura, Crocker and Denborough, 1979).

### *Measurement of adenylate kinase*

***Preparation of samples.*** Adenylate kinase was extracted from muscle biopsy samples in four volumes of Tris-HCl 5 mmol litre$^{-1}$ with Na-EDTA 0.5 mmol litre$^{-1}$ pH 8.0 unit as described by Cerri and colleagues (1981).

Red cell lysates were prepared by mixing one volume of packed cells with two volumes of water (Fildes and Harris, 1966).

*Electrophoresis.* Starch gel electrophoresis of muscle and red blood cell AK was carried out by the method described by Smith (1968), at 4 °C using a Tris–citric acid buffer, pH 7.0 unit (Schmitt, Schmidt and Ritter, 1974), and a staining solution in 1% agar (Fildes and Harris, 1966).

*AK activity.* AK activity was assayed spectrophotometrically by coupled enzyme assay systems (Fildes and Harris, 1966). Both forward (ADP utilization) and backward (ADP formation) reaction systems were used.

Protein concentration was measured by the method of Lowry and co-workers (1951).

*AK inhibitors.* Isoenzymes of AK can be distinguished by the use of inhibitors of AK activity (Khoo and Russell, 1972; Russell et al., 1974), and with this in mind the effect of the sulphydryl reacting reagents silver nitrate, M-ethylmaleimide (NEM) and p-hydroxymercuribenzoate (p-OH-MB) on the AK enzyme patterns and AK activity were assessed.

## RESULTS

### *Starch gel electrophoresis*

*Muscle.* In human muscle (and red blood cells) three distinct types of electrophoretic pattern are recognized and are referred to as AK 1, AK 2-1 and AK 2 (Fildes and Harris, 1966). About 90% of individuals in the English population have the AK 1 phenotype and about 10% have the AK 2-1 phenotype. AK 2 is very uncommon.

In the present study, the electrophoretic pattern

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of muscle AK was investigated in 10 individuals who were susceptible to MH and in 12 who were not. Each of these showed the characteristic AK 1 pattern (fig. 1A). The AK isoenzyme pattern was studied also in muscle from 15 pigs susceptible to MH and in four controls. A pattern similar to human muscle AK 1 was found in each animal (fig. 1B). However, each component in porcine AK moved faster than the component in human AK. Also, in porcine AK, the minor, faster moving components were not always clearly seen. There were no differences in the isoenzyme pattern between susceptible and control pig muscle.

*Red blood cells.* The red blood cell AK phenotype in two patients who were susceptible to MH and in two controls was AK 1 (fig. 1A). In addition, 20 blood samples from random blood donor controls were studied. One AK 2-1 phenotype was found (fig. 1A). The others were all AK 1. The AK pattern in human red blood cells was the same as in human muscle.

In porcine red blood cells the AK pattern was the same in two pigs which were susceptible to MH as in two pigs which were not. The AK pattern in porcine red blood cells was the same as in porcine muscle (fig. 1B).

*AK activity studies*

The activities which were measured spectrophotometrically in muscle are shown in table I. Greater AK activity was found in porcine samples than in human preparations, but no statistically significant differences in AK activity were found between MH-susceptible humans or swine and controls (Student's *t* test).

*Effect of specific inhibitors*

Specific inhibitors of AK invariably abolished the

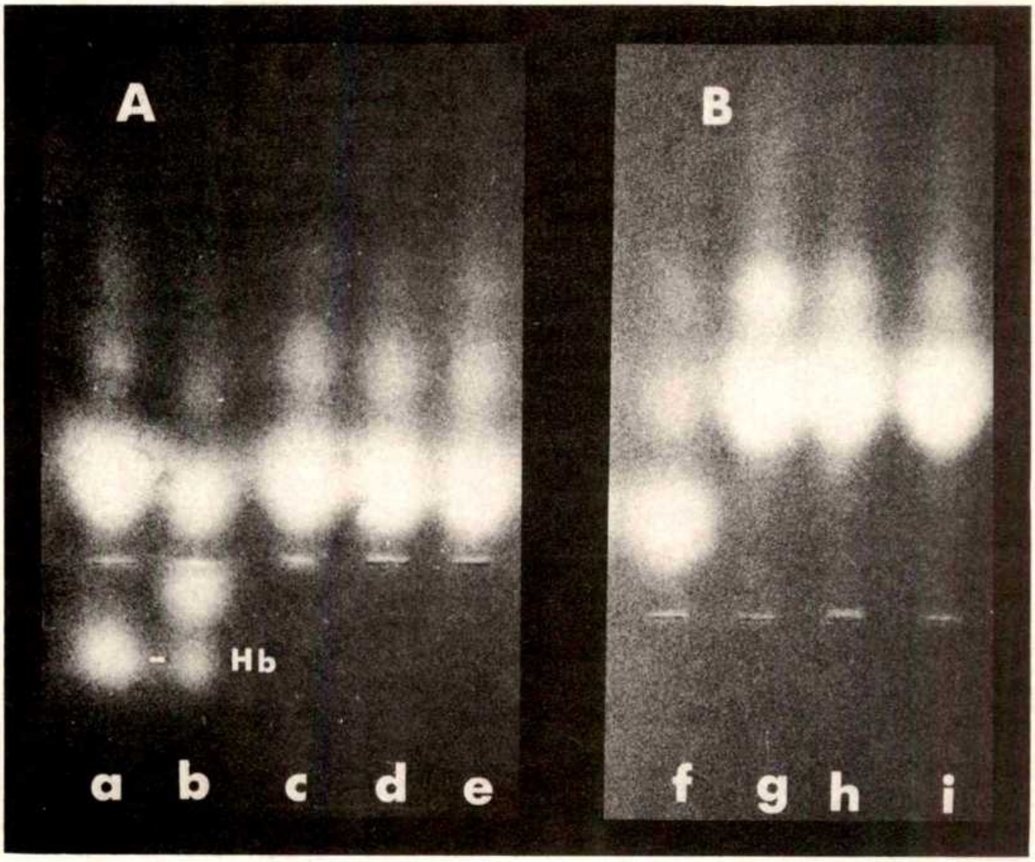

FIG. 1. Electrophoretic pattern of adenylate kinase. A: Human red blood cells and muscle—a = red blood cell AK 1; b = red blood cell AK 2-1; c–e = muscle AK (only type AK 1 observed in this study). B: Porcine muscle—f = human muscle AK (reference sample); g–i = porcine muscle AK. Hb = haemoglobin.

TABLE I. *Adenylate kinase activity in MH-susceptible and control human and porcine muscle. † Δ OD $min^{-1}$/mg protein refers to the change in optical density at 340 nm per min per mg of extracted muscle protein. *Mean values ± SD*

| Muscle | Specific activity†* (ΔOD $min^{-1}$/mg protein) | No. samples |
|---|---|---|
| Control human | 10.2 ± 4.7 | 11 |
| MH-susceptible human | 8.9 ± 3.7 | 12 |
| Control porcine | 26.4 ± 2.3 | 6 |
| MH-susceptible porcine | 23.6 ± 4.1 | 8 |

AK electrophoretic patterns and AK activity in all the samples tested, regardless of whether they were from humans or swine, and whether or not they were susceptible to MH.

## DISCUSSION

The demonstration of an abnormality in AK activity in malignant hyperpyrexia would be not only of theoretical interest but could also have considerable practical significance. The use of a simple enzyme test to screen for susceptibility to MH would be a considerable advance in the prevention of the anaesthetic complication. At present, the only definitive way to identify susceptibility to MH is to carry out a complicated *in vitro* muscle test under stringent conditions (Denborough, 1980).

The observation that adenylate kinase was deficient in a family susceptible to MH (Schmitt, Schmidt and Ritter, 1974) prompted the present investigation in which adenylate kinase activity has been examined in humans and swine which were susceptible to MH and in controls. In the present study, no deficiency in the activity or isoenzyme pattern of adenylate kinase in either skeletal muscle or red blood cells was found in MH-susceptible humans or swine. Although no statistically significant difference was observed in the present study between control and MH muscle, low AK activities were occasionally found in both groups. In these instances only the major band of the electrophoretic pattern of AK was visible, and larger amounts of samples were required to show the presence of the minor, fast-moving components.

ACKNOWLEDGEMENT

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REFERENCES

Cerri, G. G., Willner, J. H., Britt, B. A., and Wood, D. S. (1981). Adenylate kinase deficiency and malignant hyperthermia. *Human Genet.*, 57, 325.

Denborough, M. A. (1980). The pathopharmacology of malignant hyperpyrexia. *Pharmacol. Ther.*, 9, 357.

Fildes, R. A., and Harris, H. (1966). Genetically determined variation of adenylate kinase in man. *Nature (Lond.)*, 209, 261.

Harrison, G. G., Saunders, S. J., Biebuyck, J. F., Hickman, R., Dent, D. M., Weaver, V., and Terblanche, J. (1969). Anaesthetic-induced malignant hyperpyrexia and a method for its prediction. *Br. J. Anaesth.*, 41, 844.

Khoo, J. C., and Russell, P. J. (1972). Isoenzymes of adenylate kinase in human tissue. *Biochem. Biophys. Acta*, 268, 98.

Lowry, O. H., Rosebrough, N. J., Farr, A. L., and Randall, R. J. (1951). Protein measurement with the Folin phenol reagent. *J. Biol. Chem.*, 193, 265.

Moulds, R. F. W., and Denborough, M. A. (1974). Identification of susceptibility to malignant hyperpyrexia. *Br. Med. J.*, 2, 245.

Noda, L. (1973). In *The Enzymes* (ed. P. D. Boyer), vol. 8, part A, p. 279. New York: Academic Press.

Okumura, F., Crocker, B. D., and Denborough, M. A. (1979). Identification of susceptibility to malignant hyperpyrexia in swine. *Br. J. Anaesth.*, 51, 171.

Russell, P. J., Horenstein, J. M., Goins, L., Jones, D., and Laver, M. (1974). Organ specificity of adenylate kinase isoenzymes. *J. Biol. Chem.*, 279, 1874.

Schmitt, J., Schmidt, K., and Ritter, H. (1974). Hereditary malignant hyperpyrexia associated with muscle adenylate kinase deficiency. *Humangenetik*, 24, 253.

Smith, I. (1968). In *Chromatographic and Electrophoretic Techniques* (ed. I. Smith), vol. 2, p. 217. London: W. Heinemann.

## ADENYLATE KINASE ET HYPERTHERMIE MALIGNE

### RESUME

Le profil des isoenzymes et l'activité de l'adénylate kinase ont été étudiés dans le muscle et les hématies venant de patients et de porcs dont on avait prouvé qu'ils étaient prédisposés à l'hyperthermie maligne. Il n'a pas été trouvé d'anomalies du profil des isoenzymes ou de l'activité de l'adénylate kinase.

## DIE ADENYLAT-KINASE UND MALIGNE HYPERTHERMIE

### ZUSAMMENFASSUNG

Das Isoenzym-Muster und die Aktivität der Adenylat-Kinase wurden im Muskel und den roten Blutkörperchen von Menschen und Schweinen, die sich empfänglich für die maligne Hyperthermie gezeigt hatten, untersucht. Es wurde kein abnormales Enzymmuster oder abnormale Enzymaktivität gefunden.

## KINASA DE ADENILATO E HIPERPIREXIA MALIGNA

### SUMARIO

Se estudió la estructura y la actividad de la enzima kinasa de adenilato en los músculos y en los glóbulos rojos de la sangre de individuos y de cerdos que mostraron susceptibilidad a la hiperpirexia maligna. No se encontró anormalidad alguna en la estructura o actividad de dicha enzima.

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# ACUTE "TOLERANCE" TO THE CENTRAL RESPIRATORY EFFECTS OF MIDAZOLAM IN THE DOG

D. AL-KHUDHAIRI, H. ASKITOPOULOU AND J. G. WHITWAM

SUMMARY

The effect of repeated doses of midazolam 0.1 mg kg$^{-1}$ on efferent activity in the phrenic nerve was observed in seven artificially ventilated dogs, anaesthetized with chloralose and paralysed with suxamethonium. $P_{aO_2}$, $P_{aCO_2}$ arterial pH and core temperature were adjusted to constant values throughout each experiment. The first dose of midazolam caused a relatively prolonged reduction in phrenic activity, after complete recovery a second dose was administered and so on for four doses. Peak phrenic efferent activity returned to initial values on average 69.4 min after the first dose of midazolam. The effects of successive subsequent doses lasted progressively shorter times (mean values 49.4, 38.7 and 25.3 min). In four preparations, 2 h after recovery from the fourth doses a second "train" of four doses was administered. The response to the first dose of this second "train" showed that 90% recovery had occurred from the effect of the first "train" and there was a similar sequence of decreasing responses to successive doses. This study demonstrated acute tolerance to the central respiratory effects of midazolam.

Benzodiazepines cause tolerance, habituation and addiction (Hollister, Motzenbecker and Degan, 1961; Winstead et al., 1974; Greenblatt and Shader, 1978). Dissociation between, for example, the sedative and anxiolytic effects of these drugs has been reported during long-term administration (Hillestad et al., 1974; Hillestad, Hansen and Melsom, 1974) such that tolerance occurs to the sedative effects while the anxiolytic properties remain unimpaired. It has also been shown that once animals have been exposed to a benzodiazepine, conflict responses between a reward such as food, and a painful stimulus, are modified even after withdrawal of the drug for as long as observations have been made, for example up to 1 year; hence the concept of the benzodiazepine "naive" animal (Cook and Spinwall, 1975).

Forster and others (1980) have shown that the respiratory depressant effects of equipotent doses of the relatively new water soluble benzodiazepine midazolam and diazepam are comparable. It has also been reported by Whitwam and others (1980) that a dose of 2 mg kg$^{-1}$ of midazolam causes depression of activity in the phrenic nerve in anaesthetized dogs for more than 90 min. In the only previous study on acute tolerance to the effects of benzodiazepines, Barnett and Fiore (1973) showed diminished effects of repeated doses of diazepam on the linguomandibular and flexor reflexes, and depression of e.e.g. activity in cats. There are no previous studies of tolerance to the respiratory effects of the benzodiazepines.

The present study investigated the possibility of acute tolerance to the central respiratory effects of midazolam.

## METHODS

Experiments were performed on seven mongrel dogs. They were anaesthetized with methohexitone 10 mg kg$^{-1}$ administered i.v. followed by chloralose 20 mg kg$^{-1}$ h$^{-1}$, administered by continuous infusion, and intermittent suxamethonium 1–2 mg kg$^{-1}$ h$^{-1}$. They were artificially ventilated using a Starling pump via a cuffed endotracheal tube. $P_{aO_2}$, $P_{aCO_2}$, arterial pH and core temperature were in the ranges 180–220 mm Hg, 40–45 mm Hg, 7.36–7.42 units and 37–38 °C respectively. During each experiment (that is, for each preparation) these values were maintained within narrow limits and during each period of observation they were readjusted to the same values as those at the start of the experiment by changes in ventilation, $F_{IO_2}$, the administration of sodium bicarbonate and the use of heaters in the operating table.

The femoral vessels were cannulated and arterial pressure, the e.c.g. and heart rate (beat by beat Devices 5422) recorded. The phrenic nerve was

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exposed in the neck, dissected, desheathed and cut distally, immersed in mineral oil and efferent activity was recorded using bipolar silver electrodes (processed through a Tectronix 122 preamplifier and displayed on an oscilloscope, Tectronix R565 amplifier 2A63).

The activity in the phrenic nerve was integrated (Neurolog NL703). Total activity in the phrenic nerve per minute was calculated by multiplying the peak height of the integrator output by the frequency of the bursts of activity per minute. In the initial state the bursts of phrenic nerve activity were synchronized with the ventilator cycle, the rate of which was 10 b.p.m. in all experiments. Desynchronization of the phrenic nerve activity from the ventilator only occurred during the early stages of recovery from the maximum effects of the drug (figs 1 and 3). Thus by arbitrary adjustment of the peak height of the integrator output the total activity in the initial stage was similar in all preparations (hence the small SEM in fig. 2). Return to initial activity was assessed by observing the peak height of the integrator signal on the oscilloscope. For total activity per minute the peak height was multiplied by 10 (the respiratory rate) and expressed in arbitrary units (fig. 2). In the absence of drug administration the burst height remains constant for many hours provided that blood-gases and temperature are carefully controlled, and the recording electrodes remain satisfactory (that is blood and serum are not allowed to collect).

Changes in intratracheal pressure during the respiratory cycle were also recorded and were displayed on an ultraviolet recorder (SE Type 2112) together with the phrenic nerve activity and its integrated signal, the e.c.g., heart rate and femoral arterial pressure.

When stability was obtained a dose of midazolam 0.1 mg kg$^{-1}$ was administered. This initial dose of drug either abolished or greatly reduced the activity

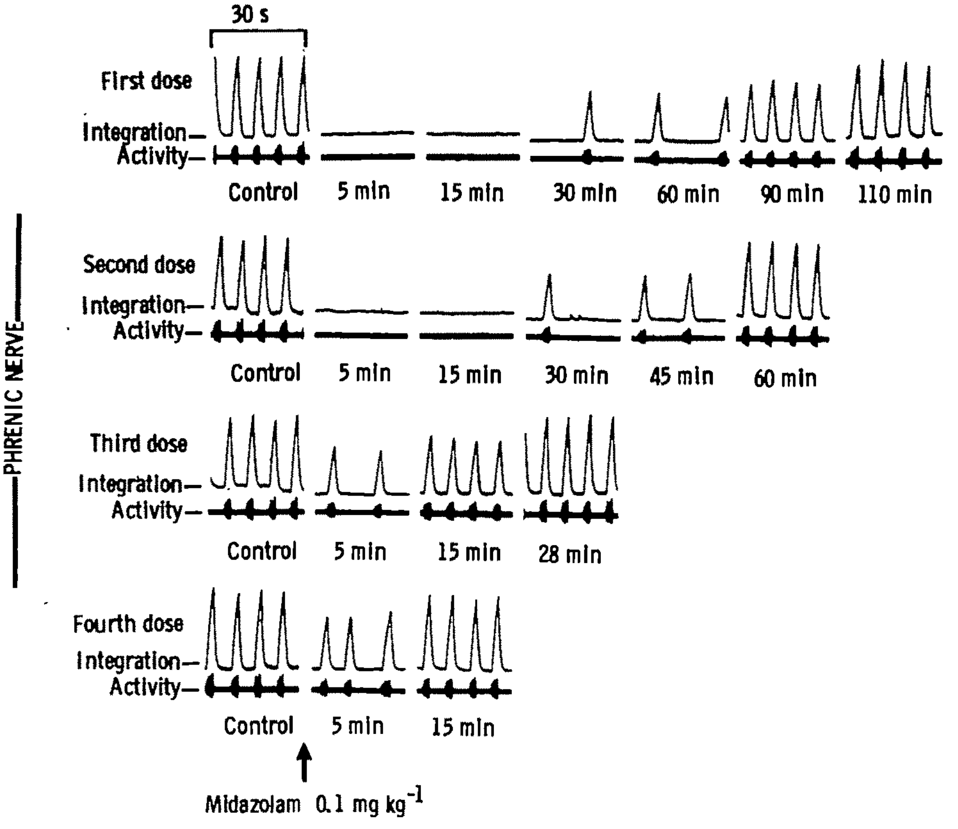

FIG. 1. Effect of repeated doses of midazolam on efferent activity in the phrenic nerve. Upper trace—first dose; lower trace—fourth dose. Successive doses were administered after recovery from the effects of the previous one.

in the phrenic nerve. When activity returned to control values, assessed by the peak height of the integrator signal, the same dose of the drug was administered and again on return to control values the dose was repeated. This sequence was repeated for a total of four doses. In the final four preparations a second "train" of four doses (0.1 mg $kg^{-1}$) was administered in a similar sequence starting 2 h after return to control values from the last dose of the first train of four doses. Statistical analysis was performed using analysis of variance and Student's $t$ test when appropriate.

## RESULTS

As with other benzodiazepines, it was found that there was a considerable variation in response between different animals to the same dose of midazolam. The maximum effect on phrenic nerve activity occurred within 80–130 s in all preparations.

The effect of four consecutive doses of midazolam on efferent activity in the phrenic nerve is shown in figure 1. It can be seen that after the first dose the activity was totally abolished by the drug, started to return at 30 min and had fully recovered by 110 min. After the second dose the sequence of events was similar. After the third dose the activity had started to return at 15 min, with total recovery at 28 min, while after the fourth dose activity was no longer totally abolished and returned by 15 min to values similar to those at the start.

The mean recovery times after each of the four doses in the seven preparations were as follows. First dose mean 69.4 min (SD 9.3 min; range 45–110 min). Second dose mean 49.4 min (SD 6.0 min; range 25–75 min). Third dose mean 38.7 min (SD 4.5 min; range 24–60 min). Fourth dose mean 25.3 min (SD 3.9 min; range 15–43 min). The mean values for the second, third and fourth doses were significantly less than the first ($P < 0.05$ in each case).

The effect of four doses of midazolam on phrenic nerve activity calculated 5, 15 and 30 min in relation to initial activity is shown in figure 2. The initial effects (at 5 min) of the second and third doses were not statistically significantly different from the first. However, the effect of the fourth dose at 5 min was significantly less than the first ($P < 0.05$). By 30 min the effects of the second, third and fourth doses were progressively less and significantly different from the first dose ($P < 0.05$ in each case).

In figure 3 the effect of a second train of four doses after a delay of 2 h from the first is seen in the same preparation as figure 1. It can be seen that a similar sequence of events occurred, and that the second, third and fourth doses in the second train had considerably less effect on the central respiratory activity than in the first.

The recovery times after the first train of four doses is compared with those of the second train in the final four preparations in figure 4. It can be seen that recovery from the tolerance induced by the first train of doses was almost complete by 2 h, so that the mean recovery time after the first dose in the second train was approximately 90% of the same value for the first train.

The haemodynamic effects of midazolam were minimal. After the first dose of the drug there was a transient decrease in arterial pressure of approximately 5%, associated with a small increase in heart rate.

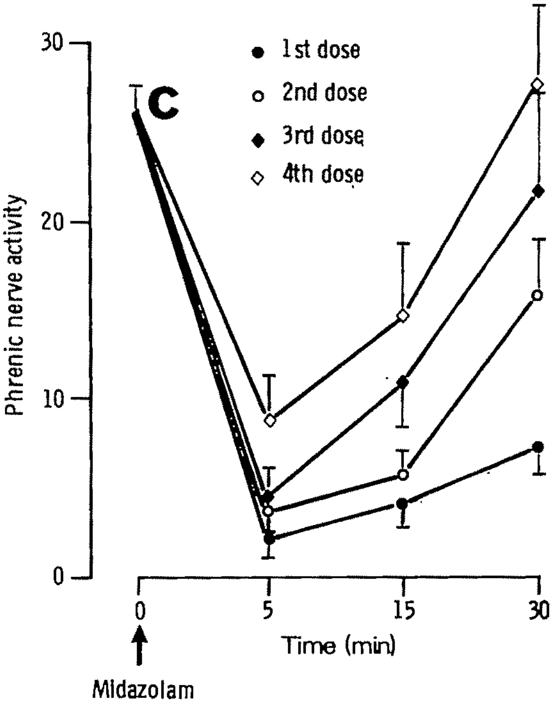

FIG. 2. Effect of repeated doses of midazolam 0.1 mg $kg^{-1}$ in seven dogs. The phrenic nerve activity was calculated as the product of the burst frequency per minute and the peak height of the integrator signal (arbitrary units) (mean ± SEM). At 5 min only the effect of the fourth dose was significantly different from the first ($P < 0.05$). At 15 min the third and fourth doses were significantly different from the first ($P < 0.05$) while at 30 min the effects of the last three doses were all significantly less than the first ($P < 0.05$, $< 0.01$ and $< 0.005$ respectively).

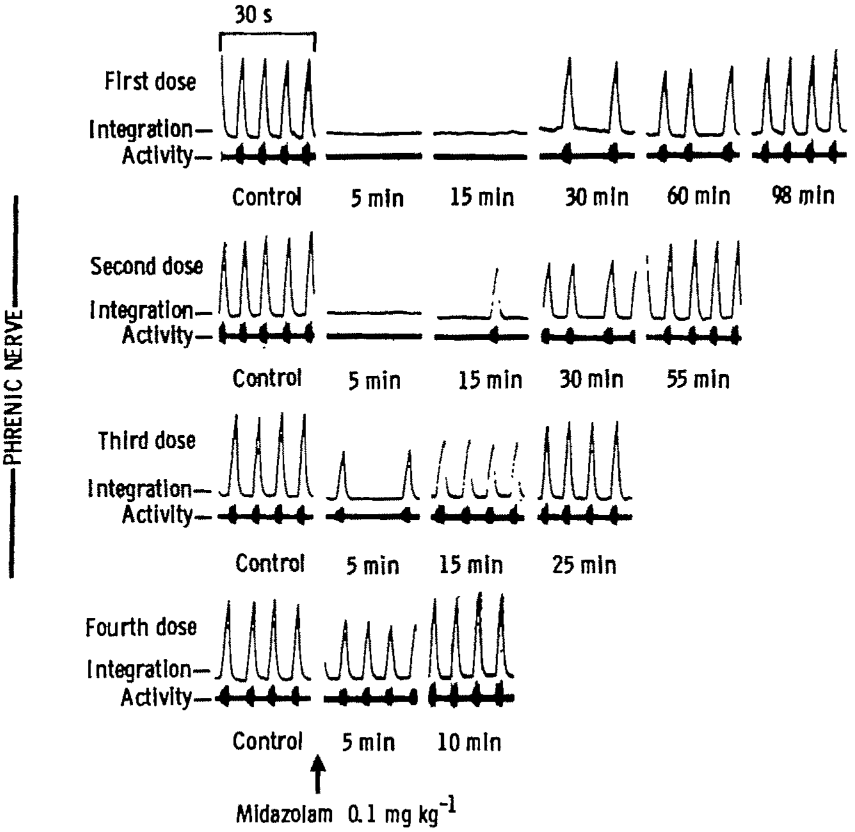

FIG. 3. Effect of a second series of four doses of midazolam 0.1 mg kg$^{-1}$ on efferent activity in the phrenic nerve commencing 2 h after complete recovery from the fourth dose of a previous sequence of four doses (0.1 mg kg$^{-1}$). Same preparation as figure 1. Upper trace—first dose; lower trace—fourth dose of the second "train" of four doses.

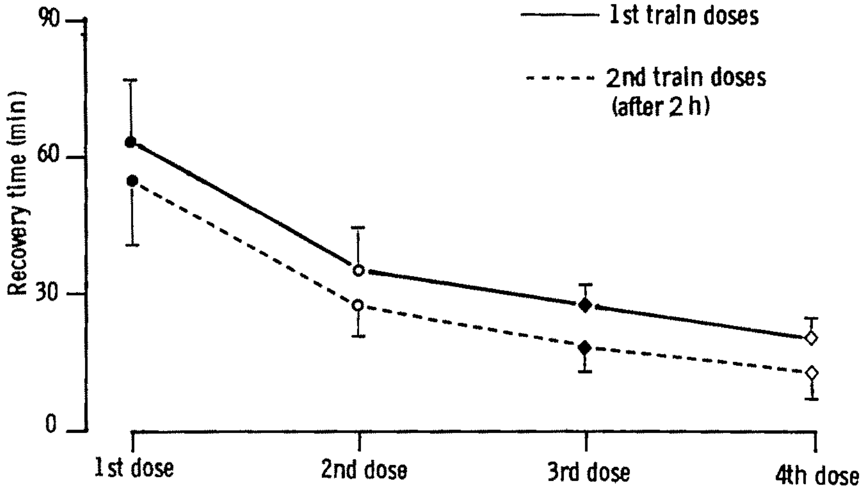

FIG. 4. Comparison of the time (mean ± SEM) for complete recovery of phrenic nerve activity after successive doses of midazolam 0.1 mg kg$^{-1}$ in four dogs. The second "train" of four doses started 2 h after complete recovery from the fourth dose of the first "train".

## DISCUSSION

The central respiratory effect of midazolam as recorded by a reduction of activity in the phrenic nerve in response to a single dose of the drug has previously been described by Whitwam and others (1980). It might be expected that midazolam would have a cumulative effect on the central nervous system when administered i.v. in repeated doses. The present study shows that in the dog anaesthetized with chloralose the reverse is true, at least for its effect on central respiratory activity. Since significant recovery of the preparation from the effects of midazolam had occurred within 2 h the term tachyphylaxis could be appropriate for this phenomenon.

In general, tolerance to drugs may be either metabolic or cellular (Greenblatt and Shader, 1974; Hillestad, Hansen and Melsom, 1974). At present there is a controversy as to whether metabolic tolerance occurs for the benzodiazepines. Greenblatt and Shader (1974) have shown that enzyme induction can occur in response to larger doses of benzodiazepine derivatives. On the other hand Vessel and others (1972) could find no evidence of such induction. It seems unlikely that in the experiments reported here the metabolism of midazolam would be so accelerated as to render the drug virtually ineffective on the fourth dose in several preparations (e.g. fig. 1). This view could be supported by the work of Klotz, Antonin and Bleck (1976), who found that the elimination half-life of diazepam following multiple doses is prolonged in comparison with a single dose, possibly as a result of an inhibitory effect of one of the metabolites (desmethydiazepam) on diazepam clearance, in spite of which acute tolerance to the effects of diazepam has been demonstrated in cats (Barnett and Fiore, 1973).

Receptors for the benzodiazepines in the central nervous system have been described (Braestrup and Squires, 1977; Mohler and Okada, 1977). Hence it could be postulated that cellular mechanisms similar to those described for the opiates (Goldstein, 1974; Clouet and Iwatsubo, 1975; Takemori, 1975) also exist for the benzodiazepines.

A naturally occurring inhibitor of benzodiazepine activity in the central nervous system has been isolated from human urine (Braestrup, Nielsen and Olsen, 1980; Braestrup and Nielsen, 1981). Barnett and Fiore (1973) have already shown that pretreatment of cats with N-desmethyldiazepam significantly interferes with diazepam-induced reflex depression. They have also suggested that acute tolerance to diazepam is the result of the formation of less potent metabolites which act at the same receptor sites as diazepam.

To establish the mechanisms responsible for the present findings would require measurements of the blood concentrations of both midazolam and its metabolites and a study of tolerance to these metabolites.

In conclusion, the present study shows development of acute tolerance to one of the actions of midazolam, namely central respiratory depression. Whether this applies to all the effects of midazolam and the mechanisms underlying this phenomenon remain to be investigated.

## REFERENCES

Barnett, A., and Fiore, J. W. (1973). Acute tolerance to diazepam in cats; in *The Benzodiazepines*, (eds S. Garratini, E. Mussini and L. O. Randall), p. 545. New York: Raven Press.

Braestrup, C., and Nielsen, M. (1981). GABA reduces binding of $^3$H-methyl $\beta$-carboline-3-carboxylate to brain benzodiazepine receptors. *Nature (Lond.)*, **294**, 472.

—— —— Olsen, C. E. (1980). Urinary and brain $\beta$-carboline-3-carboxylates as potent inhibitors of brain benzodiazepine receptors. *Proc. Natl Acad. Sci. U.S.A.*, 77, 2288.

—— Squires, R. F. (1977). Specific benzodiazepine receptors in rat brain characterised by high-affinity $^3$H diazepam binding. *Proc. Natl Acad. Sci. U.S.A.*, 74, 3805.

Clouet, D. H., and Iwatsubo, K. (1975). Mechanisms of tolerance to and dependence on narcotic analgesic drugs. *Ann. Rev. Pharmacol.*, 15, 49.

Cook, L., and Spinwall, J. (1975). Behavioural analysis of the effects and mechanisms of action of benzodiazepines. *Adv. Biochem. Psychopharmacol.*, 14, 1.

Forster, A., Gardaz, J. P., Suter, P. M., and Gemperle, M. (1980). Respiratory depression by midazolam and diazepam. *Anesthesiology*, 53, 194.

Goldstein, A. (1974). Opiate receptors. *Life Sci.*, 14, 615.

Greenblatt, D. J., and Shader, R. I. (1974). ***Benzodiazepines in** Clinical Practice*, 1st Edn, p. 242. New York: Raven Press.

—— —— (1978). Dependence, tolerance and addiction to benzodiazepines. Clinical and pharmacokinetic considerations. *Drug Metab. Rev.*, 8, 13.

Hillestad, L., Hansen, T., and Melsom, M. (1974). Diazepam metabolism in normal man. II: serum concentration and clinical effect after oral administration and cumulation. *Clin. Pharmacol. Ther.*, 16, 485.

—— —— —— Drivenes, A. (1974). Diazepam metabolism in normal man. I: serum concentrations and clinical effects after intravenous, intramuscular and oral administration. *Clin. Pharmacol. Ther.*, 16, 479.

Hollister, L. E., Motzenbecker, F. P., and Degan, R. O. (1961). Withdrawn reaction from chlordiazepoxide (Librium). *Psychopharmacologia*, 2, 63.

Klotz, U., Antonin, K. H., and Bleck, P. R. (1976). Comparison of the pharmacokinetics of diazepam after single and subchronic doses. *Eur. J. Clin. Pharmacol.*, 10, 121.

Mohler, H., and Okada, T. (1977). Benzodiazepine receptor: Demonstration in the central nervous system. *Science*, 198, 849.

Takemori, A. E. (1975). Neurochemical bases for narcotic tolerance and dependence. *Biochem. Pharmacol.*, 24, 2121.

Vessell, E. S., Passananti, G. T., Viau, J. P., Epps, J. E., and Carlo, F. J. Di (1972). Effects of chronic prazepam administration on drug metabolism in man and rat. *Pharmacology*, 7, 197.

Whitwam, J. G., Scott, W. A. C., Kurimoto, S., Orchard, C., and Chakrabarti, M. K. (1980). Cardiovascular effects of midazolam (RO-21-3981) in the dog. *Br. J. Anaesth.*, 52, 854P.

Winstead, D. K., Anderson, A., Eilers, M. K., Blackwell, B., and Zaremba, A. L. (1974). Diazepam on demand: Drug-seeking behaviour in psychiatric inpatients. *Arch. Gen. Psychiatr.*, 30, 349.

## MISE EN EVIDENCE D'UNE "TOLERANCE" AIGUE AUX EFFETS RESPIRATOIRES CENTRAUX DU MIDAZOLAM CHEZ LE CHIEN

### RESUME

Les effets de doses répétées de midazolam 0,1 mg $kg^{-1}$, sur l'activité efférente du nerf phrénique ont été étudiés chez sept chiens ventilés artificiellement, endormis au chloralose et curarisés au suxamethonium. La $Pa_{O_2}$, la $Pa_{CO_2}$ et le pH artériels ont été maintenus à des valeurs constantes pendant toute la durée des expériences. La première dose de midazolam a entraîné une réduction relativement prolongée de l'activité phrénique, après retour complet à la normale, une deuxième dose a été administrée et ainsi de suite quatre fois. Le pic d'activité phrénique efférente est revenu aux valeurs initiales en environ 69,4 min après la première dose de midazolam. Les effets des doses successives suivantes ont duré progressivement de moins en moins longtemps (valeurs moyennes: 49,4, 38,7 et 25,3 min). Dans quatre cas, un second "train" de quatre doses a été administré 2 h après le retour à des valeurs normales après la fin de la quatrième dose de la première série. La reponse à la première dose de cette seconde série a montré qu'il y avait eu une récupération de 90% par rapport aux effets de la première série, et il y avait une séquence similaire de reponses decroissantes aux doses successives. Cette étude objective une tolérance aiguë aux effets respiratoires centraux du midazolam.

## AKUTE TOLERANZ GEGENÜBER DEN AUSWIRKUNGEN VON MIDAZOLAM AUF DAS ATEMZENTRUM

### ZUSAMMENFASSUNG

Die Auswirkungen von wiederholten Dosen von Midazolam 0,1 mg $kg^{-1}$ auf die efferente Aktivität des N. Phrenicus wurde an seben künstlich beatmeten Hunden studiert, die mit Chloralose narkotisiert und mit Suxamethonium relaxiert waren. Der $Pa_{O_2}$, der $Pa_{CO_2}$ und der pH im arteriellen Blut und die Kerntemperatur wurden während des Versuches konstant gehalten. Die erste Midazolam-Dosis bewirkte eine relativ verlängerte Herabsetzung der Aktivität des N.Phrenicus. Nach vollständiger Erholung wurde eine 2 Dosis verabreicht und in derselben Weise insgesamt 4 Dosen. Die efferente Spitzenaktivität des N.Phrenicus kehrte nach der ersten Midazolamdosis im Schnitt nach 69,4 min zum Ausgangswert zurück. Die Auswirkungen der sukzessiven weiteren Dosen hielten progressiv kürzere Zeit an (Durchschnittswerte 49,0, 38,7 und 25,3 min). Bei vier Versuchen wurde 2 h nach der 4 Dosis eine zweite Folge von 4 Dosen verabreicht. Die Reaktion auf die erste Dosis dieser zweiten Folge zeigte, daß eine 90% Erholung von der Wirkung der ersten Folge eingetreten war, und es ergab sich eine ähnliche Folge von abnehmenden Antworten auf sukzessive Dosen. Diese Studie demonstrierte eine akute Toleranz von Midazolam auf das Atemzentrum.

## "TOLERACIA" AGUDA A LOS EFECTOS RESPIRATORIOS CENTRALES DEL MIDAZOLAN EN EL PERRO

### SUMARIO

Se observaron los efectos de repetidas dosis de 0,1 mg $kg^{-1}$ de midazolan en la actividad eferente del nervio frénico de siete perros artificialmente ventilados, anestesiados con cloralasa y paralizados con suxametonio. Los valores de la temperatura central, del pH arterial, de la $Pa_{CO_2}$ y de la $Pa_{O_2}$ se ajustaron a valores constantes a lo largo de la duración de cada experimento. La primera dosis de midazolan ocasionó una reducción relativamente prolongada de la actividad frénica; administrándose una segunda dosis después de la recuperación total y así sucesivamente hasta cuatro dosis. Los valores máximos de la actividad frénica eferente volvieron a los valores iniciales después de un promedio de 69,4 minutos a partir de la primera dosis de midazolan. Los efectos de las dosis sucesivas posteriores duraron intervalos de tiempo progesivamente más cortos (con valores medios de 49,4, 38,7 y 25,3 minutos). Se efectuaron cuatro preparaciones en las que a las dos horas de la recuperación de la cuarta dosis se administró una segunda "serie" de otras cuatro dosis. La respuesta a la primera dosis de esta segunda "serie" mostró que había tenido lugar una recuperación del 90% en relación al efecto de la primera "serie", obteniéndose también una secuencia similar de respuestas decrecientes a las sucesivas dosis. Este estudio demostró una tolerancia aguda a los efectos respiratorios centrales del midazolan.

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# ACUTE CENTRAL RESPIRATORY EFFECTS OF DIAZEPAM, ITS SOLVENT AND PROPYLENE GLYCOL

D. AL-KHUDHAIRI, J. G. WHITWAM AND H. ASKITOPOULOU

## SUMMARY

The effects of diazepam, its vehicle and propylene glycol on central respiratory activity recorded in the phrenic nerve was observed in anaesthetized paralysed dogs. $Pa_{O_2}$ was greater than 24 kPa. $Pa_{CO_2}$ arterial pH and core temperature were maintained within narrow limits within the normal range. Diazepam 2 mg kg$^{-1}$ caused an 80% reduction in phrenic nerve activity for more than 30 min. The vehicle present in this dose caused only a transient insignificant change in phrenic activity, a second dose of vehicle equivalent to diazepam 5 mg kg$^{-1}$ caused a 40% reduction in activity which rapidly recovered. Propylene glycol in an amount in the vehicle of doses between 2 mg kg$^{-1}$ and 20 mg kg$^{-1}$ of diazepam did not cause either depression of central respiratory activity or desynchronization of this activity from the ventilation cycle, but reflexly evoked a small transient increase in activity.

It is generally agreed that diazepam (Valium, Roche) in clinical doses usually causes only a mild degree of respiratory depression (Dundee and Wyant, 1974). What is less clear is the relative effects of the drug and the components of its formulation on respiration. For example Louis, Kutt and McDowell (1967) showed that the injection of 2 ml of dilantin solvent (40% propylene glycol and 10% ethyl alcohol in water) caused transient respiratory arrest. Bradshaw and Pleuvry (1971) suggested that deaths which occurred in mice as a result of nitrazepam could be attributed to its solvent alone and that nitrazepam and diazepam when administered without solvent caused no respiratory depression until lethal doses were reached. They stated that the solvent greatly reduced the therapeutic index for both these drugs. Sharer and Kutt (1971) observed that rapid injections of a 40% solution of propylene glycol, the main component of the diazepam solvent, caused respiratory arrest in addition to haemodynamic changes and suggested that the effects were two-thirds of those cause by equivalent volumes of a diazepam formulation containing the drug. All these experiments were performed on spontaneously breathing animals without reference to either the inspired oxygen concentration or carbon dioxide and oxygen tensions in these animals.

The present study was undertaken to clarify the relative effect of diazepam (drug and vehicle), one commercial solvent, referred to as the vehicle (the vehicle of Valium (Roche)—40% propylene glycol, 10% ethyl alcohol, 9.8% sodium benzoate, 0.24% benzoic acid, 1.5% benzyl alcohol) and propylene glycol under more controlled conditions.

## METHODS

Observations were made on 15 mongrel dogs. Anaesthesia was induced with methohexitone 10 mg kg$^{-1}$ administered as a bolus i.v., and maintained with a 1% solution of α-chloralose, initially as a bolus of 3 ml kg$^{-1}$, and subsequently by a continuous i.v. infusion (2 ml kg$^{-1}$ h$^{-1}$). They were artificially ventilated with oxygen enriched air via an endotracheal tube and muscular relaxation was maintained with suxamethonium (1–2 mg kg$^{-1}$ h$^{-1}$). Catheters were inserted into the inferior vena cava (i.v.c.) via a femoral vein, and a femoral artery.

The left phrenic nerve was exposed in the neck and part was dissected free from surrounding tissues, desheathed and cut distally, immersed in mineral oil and mounted on bipolar silver electrodes to record efferent activity which was processed through a pre-amplifier (Tektronix 122) rectified, integrated (Neurolog NL 703) and displayed.

$Pa_{O_2}$, $Pa_{CO_2}$, arterial pH and core temperature were within the ranges 24–33.3 kPa, 4.7–5.9 kPa, 7.31–7.38 units and 37–38 °C respectively. In any one preparation these values were maintained within 5% of control values throughout the experimental period.

The e.c.g., beat-by-beat heart rate, intravascular

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pressures, and intratracheal pressure were recorded. The phrenic nerve activity and its integrated signal were displayed on an oscilloscope (Tektronix 265) and an ultraviolet recorder (S.E. Laboratories type 2115).

Five dogs received diazepam 2 mg $kg^{-1}$. In five others the vehicle was administered, initially in that volume which contains a dose of diazepam 2 mg $kg^{-1}$; after 30 min a further dose of vehicle equivalent to diazepam 5 mg $kg^{-1}$ was administered. In five other dogs three doses of propylene glycol 160 mg $kg^{-1}$, 400 mg $kg^{-1}$ and 800 mg $kg^{-1}$, that is the amount in the vehicle equivalent to doses of diazepam 2 mg $kg^{-1}$, 5 mg $kg^{-1}$ and 10 mg $kg^{-1}$ respectively, were administered as a 40% solution. In one preparation an amount equivalent to a dose of 20 mg $kg^{-1}$ was administered.

All drugs were adminstered via the catheter in the i.v.c., which was flushed with 0.9% sodium chloride solution before and after each injection. The same volumes of 0.9% sodium chloride solution as those of the drug, its vehicle and propylene glycol were also administered and their effects observed. All solutions, solvents and saline were at room temperature (approximately 22 °C). The activity in the phrenic nerve was quantified by multiplying the peak height of the integrated activity by its frequency per minute.

Statistical analysis was performed with analysis of variance and Student's *t* tests where appropriate.

## RESULTS

The effects of diazepam 2 mg $kg^{-1}$ in one dog and the equivalent amount of its vehicle in another are illustrated in figures 1 and 2. Whereas the drug with its vehicle caused a rapid reduction in activity in the phrenic nerve, greater that 60%, which lasted longer than 30 min, an equivalent amount of the vehicle alone had only a slight transitory effect. The effect of diazepam 2 mg $kg^{-1}$ in five preparations, is shown in figure 3. There was a mean reduction in activity of approximately 80% within 5 min which persisted beyond 30 min. The effect of the vehicle in five preparations is shown in figure 4. After an initial dose, equivalent to 2 mg $kg^{-1}$ of diazepam there was an immediate transient reduction in activity of 13% which was not statistically significant. Thirty minutes later when a further dose, equivalent to diazepam 5 mg $kg^{-1}$ was administered, there was an immediate 49% reduction in phrenic nerve activity ($P < 0.05$) which returned to 13% of control by 5 min (n.s.) and completely recovered within 10–15 min.

The effects of propylene glycol were similar in all five preparations in which it was administered. There was never any evidence of central respiratory depression, and the only change was an evoked response, in addition to the normal respiratory phased activity, which started within 2–3 s of commencing administration and persisted up to 25 s at the two higher doses, that is only 5–10 s longer than the duration of the injection (figure 5). Even when a dose of 1600 mg $kg^{-1}$ (the amount in the solvent of a dose of diazepam 20 mg $kg^{-1}$) was administered in one dog during 25 s, there was only a disturbance of phrenic nerve activity lasting 30 s, that is only 5 s after the completion of the injection, and no true respiratory depression (fig. 6). Injections of 0.9% sodium chloride solution in volumes equivalent to those of the drug solvents and propylene glycol,

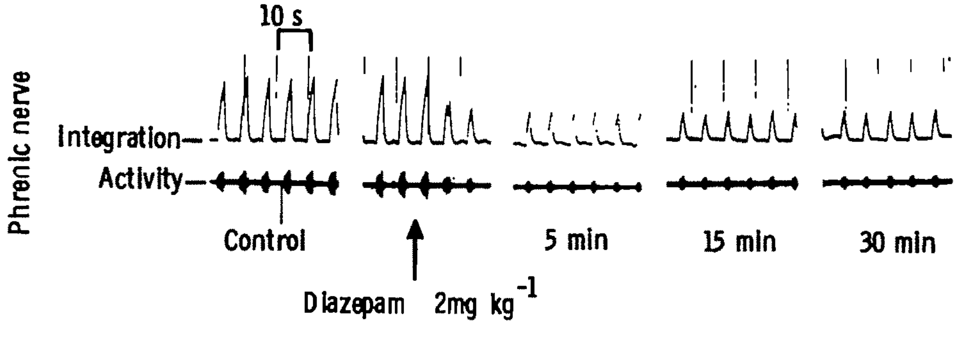

FIG. 1. Effect of diazepam on phrenic nerve activity.

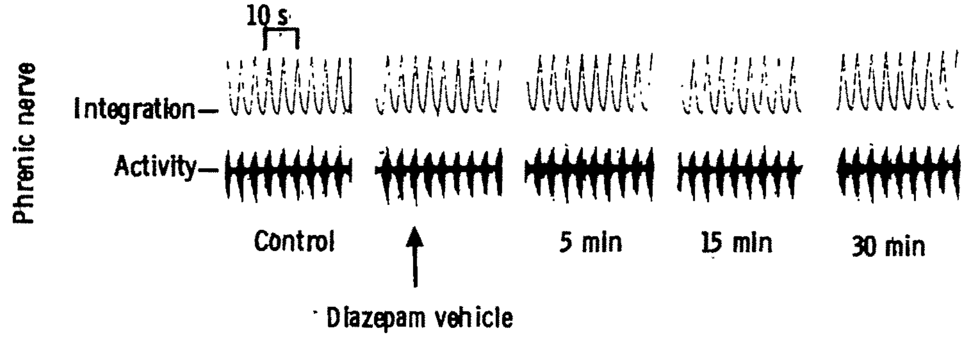

FIG. 2. Effect of diazepam vehicle on phrenic nerve activity.

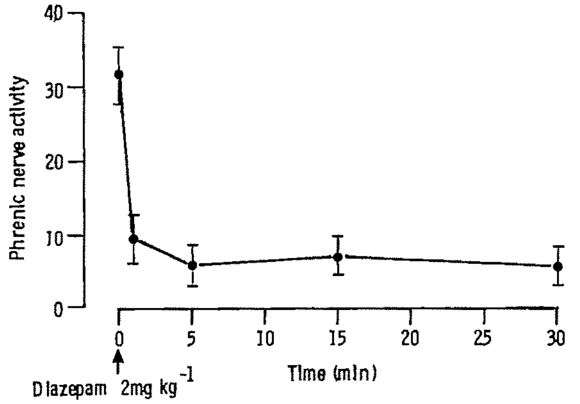

FIG. 3. Effect of diazepam on phrenic nerve activity, calculated as the product of the peak height of the integrator signal and the frequency per min of the burst of activity (mean ± SEM in five dogs).

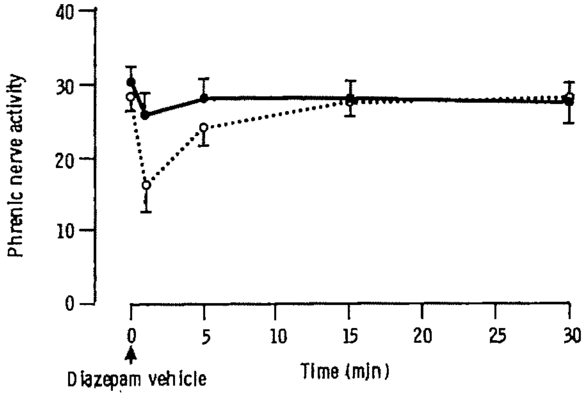

FIG. 4. Effect of diazepam vehicle on phrenic nerve activity (product of peak height and frequency per min of the integrator output) (mean ± SEM in five dogs). ●——● = Amount of vehicle equivalent to a dose of diazepam 2 mg kg$^{-1}$; ●----● vehicle equivalent to diazepam 5 mg kg$^{-1}$ administered 30 min later.

caused no demonstrable effects on central respiratory activity. Desynchronization of the normal respiratory activity from the ventilator rate did not occur.

The haemodynamic effects of diazepam, its vehicle and propylene glycol are caused by transient vagal and sympathetic reflexes, associated with changes in heart rate and arterial pressure lasting only 60–120 s, and are not relevant to the present communication (paper in preparation).

## DISCUSSION

The purpose of the present study was to demonstrate only the relative acute effects of bolus doses of diazepam, its vehicle and propylene glycol on central respiratory activity. Since the effects of the vehicle never persisted beyond 10–15 min, whereas complete recovery of these preparations, where blood-gas tensions are controlled, following a dose of 2 mg kg$^{-1}$ of diazepam may take more than 2 h, observations on the effect of the drug were terminated at 30 min.

In artifically ventilated animals, with the vagus nerves intact, activity in the phrenic nerve occurs during the expiratory pause (Tang, Maire and Amassian, 1957; Okada and Fox, 1967), the increasing activity being terminated by inflation of the lungs which could be regarded as representing the "frustration of an intended breath". Whereas in spontaneously breathing animals the peak activity of the integrated phrenic nerve signal correlates with both ventilation and muscle force output (Eldridge 1971, 1975, 1976), all that can be said of the measurement used in the present study is that it samples the state of activity of the central respiratory system, and that during both spontaneous and artificial ventilation this activity is dependent on both blood-

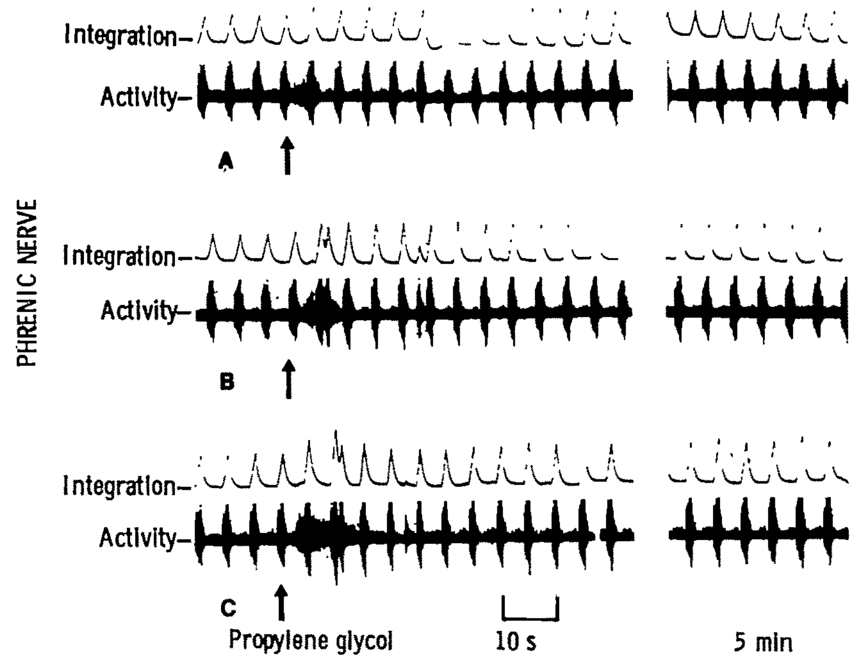

FIG. 5. Effect of a 40% solution of propylene glycol in water on phrenic nerve activity in one dog. A = 160 mg kg$^{-1}$; B = 400 mg kg$^{-1}$; C = 800 mg kg$^{-1}$ equivalent to the amounts in the vehicle of doses of diazepam 2 mg kg$^{-1}$, 5 mg kg$^{-1}$ and 10 mg kg$^{-1}$ respectively. Interval between each administration = 30 min. Injection times: A = 10 s, B = 15 s, C = 25 s.

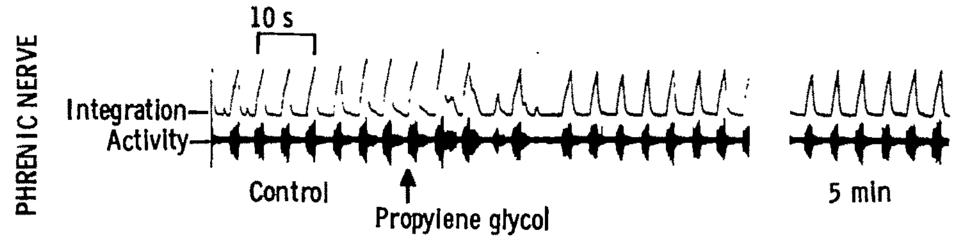

FIG. 6. Effect of propylene glycol 1600 mg kg$^{-1}$ administered as a 40% solution in water, equivalent to the amount in the vehicle of a dose of 20 mg kg$^{-1}$ of diazepam.

gas tensions and temperature (Garcia and Cherniak, 1967; Cohen and Gootman 1970; Trippenbach and Milic Emili, 1977; Ledlie et al., 1981). In the present study, $Pa_{O_2}$ was greater than the chemoreceptor threshold (Duffin, 1971) while $Pa_{CO_2}$, pH and temperature were maintained within narrow limits within the normal range. It has been shown that acute tolerance to the effects of diazepam can occur in the cat in response to its i.v. administration (Barnett and Fiore, 1973) and tolerance to the central respiratory effects of midazolam is described in the dog in an accompanying paper (Al-Khudhairi, Askitopoulou and Whitwam, 1982). Hence it is not possible to compare the effects of repeated doses of these drugs in the same preparation which should be benzodiazepine-"naive", as in the present study.

Propylene glycol can enter the pathways for carbohydrate metabolism (Ruddick, 1972) and experience suggests that this material is not cumulative and repeated doses can be studied in the same preparation (fig. 5). The onset of evoked activity in the phrenic nerve, within 2–3 s of starting the injection, and in the case of the largest doses persisting only 5 s longer than the end of the injection, must represent either a chemoreflex or one caused by noxious stimulation originating from intra thoracic structures (Dawes and Comroe, 1954). It is of interest that the timing of the onset and duration of apnoea observed by Louis, Kutt and McDowell (1967), in spontaneously breathing cats anaesthetized with intraperitoneal pentobarbitone, in response to 2 ml of dilantin solvent injected into a femoral vein, is similar.

The vehicle contains both ethyl and benzyl alcohols, the effect of which could be both cumulative and toxic in large doses and this may explain some of the observations of Bradshaw and Pleuvry (1971). In the present study the animals were "clean" only for the first injection of vehicle equivalent to 2 mg $kg^{-1}$ of diazepam, when only modest, statistically insignificant effects on central respiratory activity were observed (figs 2 and 4). The greater effect of the larger dose (fig. 4) could represent not only an increased response but also cumulation from the first dose administered 30 min previously.

In the present study there can be little doubt that diazepam caused marked and prolonged depression of central respiratory activity. It could be argued that the drug interacts with one or more of the constituents of its vehicle. However preliminary work in this laboratory on Diazemuls (Kabivitrum) indicates that the lipid solvent has no effect on central respiratory activity, whereas the whole formulation (drug and vehicle) in a dose of 2 mg $kg^{-1}$ of diazepam causes effects comparable to those described here for Valium (Roche). Moreover midazolam, a water-soluble benzodiazpeine, can cause marked depression of central respiratory activity under the same experimental conditions (Whitwam et al., 1980; Al-Khudhairi, Askitopoulou and Whitwam, 1982). Thus it is unlikely that the vehicle is necessary for diazepam to exert its effects.

It was concluded that the principal cause of central respiratory depression caused by diazepam is the drug itself and not the vehicle in which it is administered. Propylene glycol, the principal solvent in several drug formulations, does not cause central respiratory depression, even in large doses, but does appear to evoke a small transient increase in activity, the timing of which suggests a reflex origin from intrathoracic structures.

### REFERENCES

Al-Khudhairi, D., Askitopoulou, H., and Whitwam, J. G. (1982). Acute "tolerance" to the central respiratory effects of midazolam. *Br. J. Anaesth.*, **54**, 953.

Barnett, A., and Fiore, J. W. (1973). Acute tolerance to diazepam in cats; in *The Benzodiazepines*, (eds S. Garattini, E. Mussini and L. O. Randall), p. 545. New York: Raven Press.

Bradshaw, E. G., and Pleuvry, B. J. (1971). Respiratory and hypnotic effects of nitrazepam, diazepam and pentobarbitone and their solvents in the rabbit and mouse. *Br. J. Anaesth.*, **43**, 637.

Cohen, M. I., and Gootman, P. M. (1970). Periodicities in efferent discharge of splanchnic nerve in the cat. *Am. J. Physiol.*, 218, 1092.

Dawes, G. S., and Comroe, J. H. (1954). Chemoreflexes from the heart and lungs. *Phys. Rev.*, **34**, 167.

Duffin, J. (1971). The chemical regulation of ventilation. *Br. J. Anaesth.*, **26**, 142.

Dundee, J. W., and Wyant, G. M. (1974). *Intravenous Anaesthesia*, 1st edn. Edinburgh & London: Churchill Livingstone.

Eldridge, F. L. (1971). Relationship between phrenic nerve activity and ventilation. *Am. J. Physiol.*, **221**, 535.

——(1975). Relationship between respiratory nerve and muscle activity and muscle force output. *J. Appl. Physiol.*, **39**, 567.

——(1976). Quantification of electrical activity in the phrenic nerve in the study of ventilatory control. *Chest*, **70** (Suppl.), 154.

Garcia, A., and Cherniak, N. S. (1967). Integrated phrenic activity in hypercapnia and hypoxia. *Anesthesiology*, **28**, 1029.

Ledlie, J. F., Kelson, S. G., Cherniak, N. S. and Fishman, A. P. (1981). Effects of hypercapnia and hypoxia on phrenic nerve activity and respiratory timing. *J. Appl. Physiol.*, **51**, 732.

Louis, S., Kutt, H., and McDowell, F. (1967). The cardiovascular changes caused by Dilantin and its solvent. *Am. Heart J.*, **74**, 523.

Okada, H., and Fox, I. J. (1967). Respiratory grouping of abdominal sympathetic activity in the dog. *J. Physiol. (Lond.)*, **213**, 48.

Ruddick, J. A. (1972). Toxicology, metabolism and biochemistry of 1,2-propanediol. *Toxicol. Appl. Pharmacol.*, **21**, 102.

Sharer, L., and Kutt, H. (1971). Intravenous administration of diazepam. *Arch. Neurol.*, **24**, 169.

Tang, P. C., Maire, P. W., and Amassian, V. E. (1957). Respiratory influence on the vasomotor centre. *Am. J. Physiol.*, **191**, 218.

Trippenbach, T., and Milic-Emili, J. (1977). Temperature and $CO_2$ effect on phrenic activity and tracheal occlusion pressure. *J. Appl. Physiol.*, **43**, 449.

Whitwam, J. G., Scott, W. A. C., Kurimoto, S., Orchard, C., and Chakrabarti, M. K. (1980). Cardiovascular effects of midazolam (Ro 21-3981) in the dog. *Br. J. Anaesth.*, **52**, 954P.

## EFFETS RESPIRATOIRES CENTRAUX AIGUS DU DIAZEPAM, DE SON SOLVANT ET DU PROPYLENE-GLYCOL

### RESUME

Les effets du diazépam, de son solvant et du propylène-glycol sur l'activité respiratoire centrale enregistrée sur les nerfs phréniques ont été étudiés chez des chiens endormis et curarisés. La $Pa_{O_2}$ était supérieure à 24 kPa. La $Pa_{CO_2}$, le pH artériel et la température centrale ont été maintenus dans d'étroites limites de valeurs normales. Le diazépam 2 mg $kg^{-1}$ entraînait une diminution de 80% de l'activité du nerf phrénique pendant plus de 30 min. L'agent vecteur présent à cette dose n'entraînait qu'une modification transitoire insignifiante de l'activité phrénique, et une

deuxième dose de vecteur équivalente à 5 mg kg$^{-1}$ de diazépam entraînait une diminution de 40% de l'activité rapidement régressive. Le propylène-glycol, en quantité dans le vecteur équivalente à des doses de 2–20 mg kg$^{-1}$ de diazépam n'entraînait ni dépression de l'activité respiratoire centrale ni désynchronisation de cette activité par rapport au cycle ventilatoire, mais induisait de façon réflexe une légère augmentation transitoire d'activité.

## AKUTE WIRKUNGEN VON DIAZEPAM, SEINEM LÖSUNGSMITTEL UND VON PROPYLENGLYKOL AUF DAS ATEMZENTRUM

### ZUSAMMENFASSUNG

Die Wirkung von Diazepam, seinem Lösungsmittel und Propylenglykol auf das zentrale Atemzentrum, am N.Phrenicus aufgezeichnet, wurde an narkotisierten und relaxierten Hunden untersucht. Der $P\text{a}_{\text{O}_2}$ war großer als 24 kPa, und der $P\text{a}_{\text{CO}_2}$ im arteriellen Blut sowie die Kerntemperatur wurden innerhalb enger Grenzen im Normbereich gehalten. Diazepam 2 mg kg$^{-1}$ bewirkte eine 80%-ige Herabsetzung der Aktivität des N.Phrenicus für über 30 min. Das bei dieser Dosis vorhandene Lösungsmittel verursachte nur eine vorübergehende nichtsignifikante Veränderung der Phrenikusaktivität. Die 2 Dosis des Lösungsmittels äquivalent zu 5 mg kg$^{-1}$ Diazepam äquivalentem Lösungsmittel führte zu einer 40%-igen Herabsetzung der Aktivität, die sich rach wieder erholte. Propylenglykol, in einer Menge, wie er im Lösungsmittel von Dosen zwischen 2 mg kg$^{-1}$ und 20 mg kg$^{-1}$ Diazepam enthalten ist, verursachte weder eine zentrale Atemdepression noch eine Desynchronisation des Atemzyklus, sondern bewirkte einen reflektorischen, vorübergehenden geringen Anstieg der Atemtätigkeit.

## EFECTOS AGUDOS SOBRE LA ACTIVIDAD RESPIRATORIA CENTRAL POR PARTE DEL DIAZEPAN, DE SU SOLVENTE Y DEL GLICOL DE PROPILENO

### SUMARIO

Se observaron los efectos del diazepan, de su portador y del glicol de propileno sobre la actividad respiratoria central registrada en el nervio frénico de perros anestesiados y paralizados. La $\text{Pa}_{\text{O}_2}$ fue superior a 24 kPa. La temperatura central y el pH arterial de $\text{Pa}_{\text{CO}_2}$ se mantuvieron constantes en el marco de los reducidos límites de la gama normal. 2 mg kg$^{-1}$ dieron lugar a una reducción del 80% en la actividad del nervio frénico por espacio de más de 30 minutos. El disolvente portador de esta dosis causó tan sólo una alteración momentánea e insignificante en la actividad frénica; una segunda dosis de este portador que fue equivalente a 5 mg kg$^{-1}$ de diazepan motivó una reducción del 40% en la actividad que se recuperó rápidamente. Cantidades de glicol de propileno equivalentes a un valor comprendido entre 2 mg kg$^{-1}$ y 20 mg kg$^{-1}$ de diazepan, por medio del mismo portador, no ocasionaron depresión de la actividad respiratoria central ni la deshidratación de esta actividad en lo tocante al ciclo de ventilación, pero evocó de una forma refleja un ligero incremento momentáneo de la actividad.

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# INTERACTION BETWEEN REGIONAL MYOCARDIAL ISCHAEMIA AND LEFT VENTRICULAR PERFORMANCE UNDER HALOTHANE ANAESTHESIA*

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## SUMMARY

The effect of halothane on the performance of myocardium supplied by a narrowed coronary artery has been assessed in an attempt to examine the influence of halothane on hearts with non-occlusive coronary artery disease. The study was divided into two parts: first, the left anterior descending (LAD) coronary artery was constricted beyond its second diagonal branch and, second, the left circumflex (LC) was constricted close to its origin. In both parts, the myocardium was exposed to stepwise increases in inspired halothane before and after critical constriction of the vessel under study. Deepening halothane anaesthesia led to a dose-dependent depression of regional and global myocardial performance before critical constriction. After constriction, ischaemic changes in the contraction pattern of myocardium with a limited blood supply were noted. If the ischaemia was confined to a small area of the heart (LAD stenosis) there was no significant deterioration of global LV performance. However, widespread ishchaemia (LC stenosis) led to irreversible heart failure in four of the five animals studied.

The negative inotropic effect of halothane on the myocardium is well established and has been demonstrated in isolated heart muscle preparations (Goldberg and Ullrick, 1967; Sugai, Shimosato and Etsten, 1968; Brown and Crout, 1971), the intact heart in a variety of experimental animal preparations (Prys-Roberts et al., 1972; Vatner and Smith, 1974; Merin, Verdouw and de Jong, 1977) and in man (Eger et al., 1970; Prys-Roberts et al., 1974; Sonntag et al., 1978, 1979). However, the influence of halothane on ischaemic myocardium is not as well defined and controversy remains as to whether halothane anaesthesia is beneficial to the patient with ischaemic heart disease (Merin, 1980). Experimental work considering the interaction of halothane and the ischaemic myocardium has mostly been performed in hearts in which ischaemia was produced by coronary artery occlusion. Under these circumstances, halothane has been shown to decrease the severity and extent of myocardial ischaemia (Bland and Lowenstein, 1976; Davis et al., 1979) ostensibly by improving the ratio of oxygen supply to demand in the ischaemic area (Smith, Rogers and Thorburn, 1980). However, models of acute coronary arterial occlusion may be inappropriate for myocardium in which blood supply is limited and which may become ischaemic when stressed, as occurs in clinical coronary artery disease. In addition, no attempt was made with previous models to assess directly the contractile performance of the ischaemic myocardium. The model used in this study involved imposing a critical constriction on a coronary artery and assessing subendocardial shortening by the continuous measurement of segment length using ultrasound.

Initial work with this model demonstrated that halothane caused an exaggerated depression of regional myocardial performance in areas of myocardium supplied by a narrowed coronary artery. This was thought to be a result of the development of ischaemia, since the contraction patterns which were observed were similar to those described after coronary arterial occlusion. Myocardium with an undisturbed blood supply was depressed in a dose-dependent fashion without any major modification in contraction pattern (Lowenstein et al., 1981). The mass of ischaemic muscle under study was small and its dysfunction remained undetected by pressure-based indices of global ventricular perfor-

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mance. The present study extends these observations by: (i) examining whether the performance of the heart as a pump is adversely affected by the development of ischaemia in a small area of myocardium; (ii) constricting a coronary artery, which supplies a large area of myocardium, to determine the relationship between the mass of ischaemic muscle and the degree of impairment of global ventricular performance and, (iii) measuring coronary blood flow to confirm that ischaemia is the cause of the severe depression of shortening observed under halothane anaesthesia in myocardium with a reduced blood supply.

## METHOD

Twelve mongrel dogs weighing between 14 and 30 kg were studied in two groups. In the first group ($n = 7$) the left anterior descending coronary artery (LAD) was constricted distal to the second diagonal branch. In the second ($n = 5$), the left circumflex coronary artery (LC) was constricted close to its origin. The anaesthetic management and surgical procedure used were the same in both groups. The dogs were premedicated with morphine sulphate 1.5 mg $kg^{-1}$. Anaesthesia was induced with thiopentone 15 mg $kg^{-1}$, the trachea intubated and constant volume IPPV commenced at a rate of 12 b.p.m. and a tidal volume of 40 ml $kg^{-1}$. The inspired gas mixture was 1% halothane in 70% oxygen in nitrogen with sufficient carbon dioxide added to maintain end-tidal carbon dioxide at 5.3% as indicated by an infra-red carbon dioxide analyser. The halothane was supplied by a Fluotec vaporizer (Cyprane Ltd, Keighley, England) the calibration of which was checked with a Riken refractometer. A thermistor probe was inserted into the mid-oesophagus and the temperature measured with a digital thermometer. A heating element, incorporated into the operating table, maintained body temperature between 37 °C and 38 °C.

The left common carotid artery was exposed in the neck and a stiff 14-gauge polyethylene catheter (Portex Ltd, 30 cm, 8 French gauge 200/300/070) was introduced and advanced to within 1 cm of the aortic valve. This allowed the measurement of systemic arterial pressure, after connection to a Statham P23 De strain gauge transducer, and the withdrawal of blood samples. A similar cannula was threaded into the inferior vena cava from a hind limb vein for the continuous infusion of saline at an hourly rate of 4 ml $kg^{-1}$. Lead II of the electrocardiogram was recorded throughout each experiment.

A left lateral thoracotomy was performed through the fifth and sixth ribs and the pericardium opened. The fat pad at the root of the aorta was dissected away and an electromagnetic flow probe (SEM 230 SE Laboratories) placed around the vessel. A miniature Konigsberg implantable pressure transducer (P19, Konigsberg Instruments, Inc., Pasadena, California, U.S.A.) was inserted into the cavity of the left ventricle via an incision in the apical dimple. A cannula (Portex Ltd, umbilical cannula, 35 cm, 6 French gauge 200/105/060) was inserted into the left atrial appendage and connected to a CEC strain gauge transducer (Type 4-327 L221, Bell and Howell, Consolidated Electrodynamics Division, Basingstoke, U.K.) to allow measurement of left atrial pressure. A similar cannula was inserted into the pulmonary artery for the injection of indocyanine green during an *in vivo* calibration of the flowmeter system by the dye dilution method for estimating cardiac output. A pericardial cradle was then constructed before the coronary artery to be narrowed was dissected free and a 3-0 Dacron thread placed around the vessel. The thread was later attached to a micrometer and used to constrict the vessel. In group 2, left circumflex coronary flow was measured by placing an electromagnetic flow probe (SEM 230 SE Laboratories) around the vessel. A pneumatic occluder was positioned distal to the probe so that zero flow readings could be obtained.

The methods used for calibrating the pressure transducers have been described previously (Roberts et al., 1976). The left ventricular pressure (LVP) signal was fed to an analog differentiator to derive LV $dP/dt$ (Gersh, Hahn and Prys-Roberts, 1971). The aortic flow signal was passed to an analog integrator comparator and differentiator to derive stroke volume (SV) and aortic blood acceleration ($dQ/dt$) respectively (Roberts et al., 1976).

Two pairs of ultrasonic crystals (1.5–2 mm in diameter) were implanted at subendocardial level in the minor axis of the heart so that one pair was located in an area supplied by the LAD and another in an area supplied by the LC. The theory of ultrasonic length measurement has been well described (Franklin et al., 1973; Theroux et al., 1974; Hagl et al., 1977). The distance between a pair of crystals is proportional to the transit time of ultrasound because ultrasound has a constant velocity of 1.56 mm $\mu s^{-1}$ in myocardium. A continuous analog signal of dynamic segment length is provided by a repetition rate of 1 kHz. The measured transit time was calibrated in steps of 1 $\mu s$ generated by an accurate quartz-controlled oscillator.

The following variables were recorded on a Mingograf 81 eight-channel recorder (Elema Schonander, Stockholm, Solna, Sweden): e.c.g., aortic, left ventricular and left atrial pressures, LV d*P*/d*t*, aortic blood flow, stroke volume, aortic blood acceleration, coronary blood flow and the two length signals. This was achieved by sequential switching of the recording channels. A 1-h period of stabilization was allowed after the surgical preparation of the animal was complete.

### EXPERIMENTAL DESIGN

The aim of each experiment was to expose the myocardium to stepwise increases in inspired halothane concentration before and after critical constriction of either the LAD (distal to its second diagonal branch) in group 1 or the LC (close to its origin) in group 2. Thus, the area of myocardium supplied by the narrowed coronary artery beyond the point of constriction was much greater in group 2. The experimental design used in the two groups will be described separately.

#### *Group 1: Left anterior descending stenosis* (n = 7)

A halothane challenge was carried out by increasing the inspired halothane concentration in steps of 0.5% from 0.5% up to 2%. If the inspired halothane concentration had been greater than 0.5% before the challenge it was decreased to that concentration for 10 min. Recordings were obtained during a 20-s period of apnoea after 10 min at each concentration of halothane. The animal was then maintained at 0.5% halothane for 20 min before applying the critical constriction. The artery was narrowed by tightening the micrometer-controlled snare to a point where any further narrowing of the vessel produced segmental contraction abnormalities. A hypoxia test was carried out to determine whether this level of constriction was critical. The animal was ventilated with 100% nitrogen without change of $F_{ICO_2}$ or halothane concentration for 90 s. The constriction was considered to be critical if the muscle segment supplied by the narrowed artery contracted abnormally whilst the contraction of the control segment remained normal. Twenty minutes were allowed before carrying out a second halothane challenge in the same manner as described above.

#### *Group 2: Left circumflex stenosis* (n = 5)

The concentrations of inspired halothane used for each halothane challenge were 0.5, 1.0, 1.25, 1.5, 1.75 and 2.0%. As in group 1, if the inspired halothane concentration had been greater than 0.5% before the challenge it was decreased to that concentration for 10 min. All measurements were taken from beats at end-expiration after 10 min at each inspired concentration.

Critical constriction was applied in exactly the same way as in group 1 and was deemed to be critical if the degree of narrowing applied was such that 95% of the hyperaemic response to a 10-s occlusion of the vessel was abolished. The normal hyperaemic response was measured before the artery was narrowed. The vessel was then narrowed using the snare until a point was reached where any further narrowing of the vessel produced contraction abnormalities. Critical constriction was confirmed if a further 10-s occlusion of the artery abolished 95% of the previously measured hyperaemic response. Twenty minutes were again allowed before carrying out the second halothane challenge in the same way as the first.

At the end of the experiment the artery was cannulated proximal to the flow probe. Evans Blue dye was then injected to determine the mass of muscle supplied by the artery.

### ANALYSIS OF THE ULTRASONIC LENGTH SIGNAL

#### *Description of normal wall motion*

Figure 1 (left hand panel) shows a normal length trace in relation to the recorded haemodynamic variables. There is a small increase in segment length at the end of diastole, as a result of atrial contraction. The end-diastolic length (EDL) is measured at the beginning of the sharp upslope of LV d*P*/d*t* although the length from which the muscle contracts may be greater than EDL ($L_{max}$). The end-systolic length (ESL) is measured at the time of aortic valve closure, as indicated by the cessation of aortic flow. However, the muscle may contract to its shortest length before the end of systole ($L_{min}$).

#### *Description of abnormal wall motion*

Figure 1 (right hand panel) illustrates abnormal wall motion, which is typical of severe ischaemia (Theroux et al., 1974). It is characterized by the segment lengthening during systole followed by shortening in early diastole (post-systolic shortening, PSS). In this laboratory, the length to which the muscle shortens in diastole has been termed $L_{min}$D. An easily quantified index of paradoxical wall motion is PSS, which is calculated from the interval ESL − $L_{min}$D.

*Quantification of segmental shortening*

In any analysis of segmental shortening, it is immediately clear that the distance apart that the crystals are inserted is arbitrary and primarily governed by the surface anatomy of the myocardium. Thus, it is important that the shortening data should be normalized. This can be achieved in two ways:

(a) All individual length measurements can be divided by the EDL at the start of the experiment and multiplied by 10, so that the distance apart the crystals are inserted is normalized to 10 mm (Theroux et al., 1974). This method is important if the shortening data are to be expressed as an interval or if individual length measurements are to be considered.

(b) The shortening data can be expressed as a percentage by dividing the interval of shortening by the length from which shortening occurred. We have chosen to analyse the greatest interval of systolic shortening ($L_{max} - L_{min}$) and to divide this by $L_{max}$, as this, and not EDL, is the length from which the muscle contracts.

COMPUTATIONS

The data were manually digitized and subsequently stored and analysed on a Hewlett-Packard calculator 9825A.

Mean arterial pressure (m.a.p.) was calculated from the systolic and diastolic systemic arterial pressures (s.a.p. and d.a.p.).

Coronary perfusion pressure (c.p.p.) was calculated in the conventional fashion as the difference between d.a.p. and left ventricular end-diastolic pressure (l.v.e.d.p.).

Systemic vascular resistance was determined from the ratio of m.a.p. to cardiac output, neglecting mean right atrial pressure (McDonald, 1974).

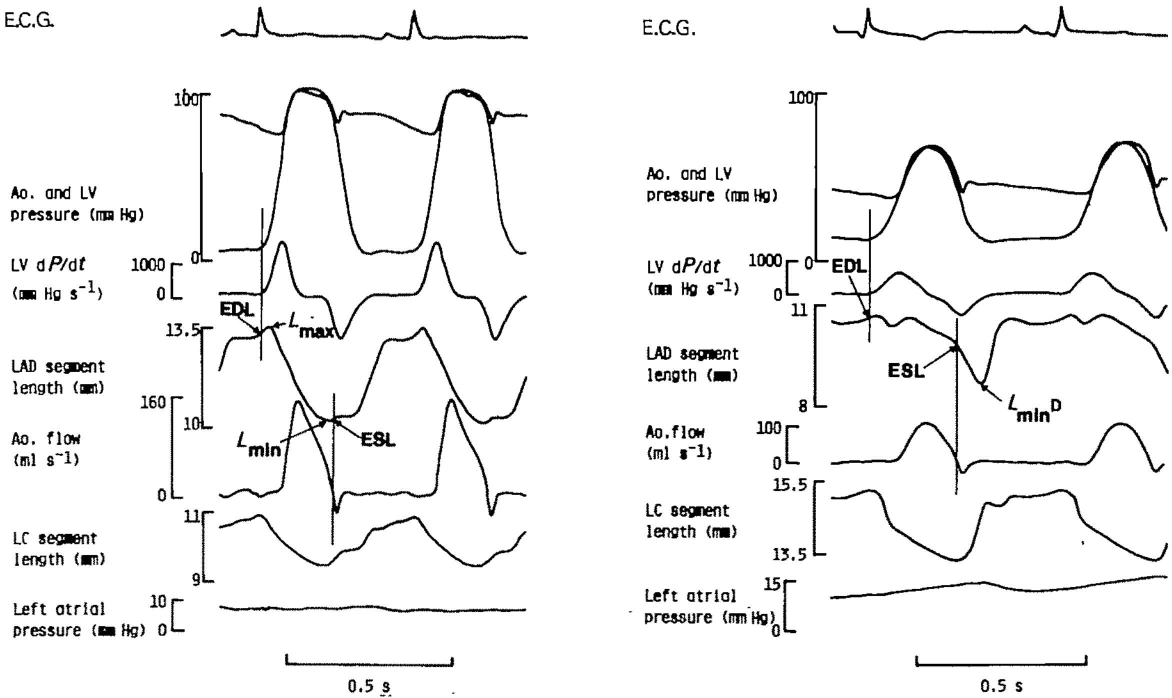

FIG. 1. A normal length trace, in relation to other haemodynamic variables which were recorded, is illustrated in the left hand panel. The end-diastolic length (EDL) was measured at the beginning of the sharp upslope of LV d*P*/d*t*, although the length from which the muscle contracts may be greater than EDL($L_{max}$). The end-systolic length (ESL) was measured at the time of cessation of aortic flow but it was noted that the muscle may contract to its shortest length before the end of systole ($L_{min}$). An ischaemic length trace, taken from a dog in group 1 (LAD stenosis) under 2% halothane anaesthesia and with critical constriction of the LAD coronary artery, is illustrated in the right-hand panel. Lengthening occurs during systole and the muscle shortens in early diastole. The length to which the muscle shortens in diastole has been termed $L_{min}$D in this laboratory.

Left ventricular stroke work (l.v.s.w.) was calculated from the product of m.a.p. and stroke volume.

All results were analysed for statistical significance using Student's paired *t* test.

## RESULTS

Severe depression of contractile function, marked by ischaemic changes in contraction pattern, was observed in myocardium supplied by a narrowed artery at deeper levels of halothane anaesthesia. Ischaemia confined to a small area of the heart (group 1) was not reflected in any index of global ventricular performance. However, widespread ischaemia (group 2) led to irreversible heart failure in four of the five animals which were studied. The mass of muscle supplied by the LC coronary artery comprised 47 ± 4% of the free left ventricular wall. The effect of halothane on the performance of the myocardium after constriction of LAD (group 1) was determined by making paired comparisons on the data at the same inspired concentrations before and after critical constriction. This was not possible for the data obtained from group 2, since irreversible failure occurred at different inspired concentrations of halothane (two animals died at 1.75% and two at 2%). This problem was overcome by identifying three stages during the halothane challenge carried out after critical constriction. These were: (i) the control stage, (ii) the last stage at which contraction in the LC segment was normal, and (iii) the last stage at which meaningful measurements were made. The mean concentrations for stages 2 and 3 were 1.35 ± 0.16% and 1.9 ± 0.06% respectively. Paired comparisons between the data were then made before and after constriction at the three concentrations of inspired halothane which had been identified.

The results from the two groups of experiments will be described together. Individual length measurements are presented in their normalized form (see Methods).

### *Influence of halothane on normal myocardium*

*Length data (tables I and II)*

A dose-dependent increase in the individual length measurements (EDL, $L_{\max}$, $L_{\min}$ and ESL) was seen in both segments. The increases in $L_{\min}$ and ESL were greater than those of EDL and $L_{\max}$, so that there was a dose-dependent reduction of shortening. The LAD segment was more dynamic than the LC in both groups, although, in group 1, the percentage reduction in shortening was the same for both segments (table I). In group 2, the LC segment was considerably less depressed than the LAD (table II). At no stage were ischaemic changes observed in either segment.

*Haemodynamic data (tables III and IV)*

(a) *Pressure-based indices of ventricular performance.* Mean arterial pressure (m.a.p.) and coronary perfusion pressure (c.p.p.) decreased progressively and significantly whilst left ventricular end-diastolic pressure (l.v.e.d.p.) was significantly increased. LV $dP/dt_{\max}$ was also decreased in a significant dose-dependent fashion.

(b) *Flow-derived indices of ventricular performance.* Cardiac output (CO), peak aortic blood acceleration ($dQ/dt_{\max}$), left ventricular stroke work (l.v.s.w.) and coronary blood flow (group 2) were all decreased in a significant dose-dependent fashion. No significant changes were observed in systemic vascular resistance (SVR).

### *Influence of halothane on myocardium with a reduced blood supply*

*Length data (tables I and II)*

The dose-dependent effects of halothane on regional performance were again seen, although these changes were modified by the onset of ischaemia. The two segments will be considered as the control segment and the ischaemic segment. Thus, in group 1, the ischaemic segment was the LAD and, in group 2, it was the LC.

*Ischaemic segment.* In five of the seven animals in group 1 and all of the animals in group 2, the segment supplied by the narrowed artery became ischaemic. $L_{\min}$ and ESL were significantly increased and shortening significantly decreased at the greatest inspired halothane concentration. The greater reduction of shortening was a reflection of the severe impairment of contraction which was evident as ischaemia progressed and is illustrated in the upper left hand panels of figures 2 and 3. Figure 1 (right hand panel) shows an ischaemic contraction pattern. Shortening after valve closure (post-systolic shortening, PSS) is a striking feature of ischaemic contraction and can easily be quantified. This can be demonstrated in those segments which became ischaemic. In figure 4, increase in PSS has been plotted against the different stages of the experiment. It can be seen that after constriction PSS was significantly increased in the ischaemic segment of

TABLE I. *Effect of increasing halothane concentration upon regional ventricular function before and during constriction of the left anterior descending coronary artery in dogs.* (n = 7). *Values are mean ± SEM for the segment supplied by the left anterior descending coronary artery (LAD) and the left circumflex coronary artery (LC). EDL = end diastolic length;* $L_{max}$ *= length from which muscle contracts;* $L_{min}$ *= minimum length during systole; ESL = end-systolic length. Statistical significance symbols refer to paired Student's* t *tests: (a) comparison with pre-constriction or constriction control:* *$P < 0.05$, **$P < 0.01$, ***$P < 0.005$, ****$P < 0.001$. *(b) Comparison with same inspired concentration preconstriction:* †$P < 0.05$, ††$P < 0.01$

| | Before constriction | | | | During constriction | | | |
|---|---|---|---|---|---|---|---|---|
| | Halothane (%) | | | | Halothane (%) | | | |
| | 0.5 | 1.0 | 1.5 | 2.0 | 0.5 | 1.0 | 1.5 | 2.0 |
| LAD | | | | | | | | |
| EDL (mm) | 10.0 | 10.0<br>(0.07) | 10.07<br>(0.08) | 10.25*<br>(0.08) | 10.06<br>(0.14) | 10.09<br>(0.10) | 10.28<br>(0.14) | 10.60<br>(0.16) |
| $L_{max}$ (mm) | 10.1<br>(0.03) | 10.08<br>(0.08) | 10.15<br>(0.10) | 10.33*<br>(0.09) | 10.18<br>(0.14) | 10.20<br>(0.11) | 10.36<br>(0.13) | 10.66<br>(0.16) |
| $L_{min}$ (mm) | 8.07<br>(0.14) | 8.13<br>(0.15) | 8.40**<br>(0.14) | 8.74***<br>(0.18) | 8.32<br>(0.16) | 8.51<br>(0.11) | 8.95<br>(0.25) | 9.78*†<br>(0.38) |
| ESL (mm) | 8.26<br>(0.17) | 8.33<br>(0.16) | 8.61*<br>(0.16) | 8.87***<br>(0.19) | 8.38<br>(0.18) | 8.57<br>(0.13) | 9.05<br>(0.23) | 9.87*<br>(0.36) |
| % Shortening | 20.1<br>(1.3) | 19.4*<br>(1.2) | 17.2***<br>(1.4) | 15.4****<br>(1.4) | 18.3†<br>(1.4) | 16.6*††<br>(1.3) | 13.6*<br>(1.9) | 8.3***†<br>(2.7) |
| LC | | | | | | | | |
| EDL (mm) | 10.0 | 10.09<br>(0.05) | 10.14*<br>(0.04) | 10.30****<br>(0.02) | 10.20<br>(0.15) | 10.22<br>(0.14) | 10.31<br>(0.14) | 10.60*<br>(0.19) |
| $L_{max}$ (mm) | 10.06<br>(0.03) | 10.13<br>(0.04) | 10.18*<br>(0.03) | 10.32****<br>(0.02) | 10.24<br>(0.17) | 10.26<br>(0.17) | 10.34<br>(0.14) | 10.62*<br>(0.20) |
| $L_{min}$ (mm) | 8.80<br>(0.04) | 8.93*<br>(0.05) | 9.04*<br>(0.07) | 9.29****<br>(0.09) | 8.98<br>(0.13) | 9.03*<br>(0.12) | 9.16***<br>(0.11) | 9.56*<br>(0.15) |
| ESL (mm) | 8.98<br>(0.07) | 9.07<br>(0.08) | 9.20<br>(0.12) | 9.42***<br>(0.13) | 9.05<br>(0.15) | 9.11<br>(0.14) | 9.25***<br>(0.14) | 9.65*<br>(0.19) |
| % Shortening | 12.5<br>(0.5) | 11.9<br>(0.7) | 11.2*<br>(0.7) | 9.9**<br>(0.9) | 12.2<br>(0.7) | 12.0<br>(0.8) | 11.3<br>(0.8) | 9.9<br>(1.7) |

group 1. Such changes were not seen in the control segment. The increase in PSS in group 2 was small in comparison despite a severe reduction in shortening.

*Control segment.* In two dogs in groups 1 and in all the dogs in group 2 the onset of ischaemia led to an increase in shortening in the control segment. Thus, in these dogs, the degree of depression of shortening after constriction was less than that noted before at the same inspired concentration of halothane. This improvement in shortening is well illustrated in figure 3, in which it can be seen that the depression of shortening in the LAD (non-ischaemic territory) at stage 3 is less after constriction than before.

*Haemodynamic data*

The dose-dependent changes in haemodynamics described before constriction were also observed after constriction. At the beginning of the second halothane challenge the flow-derived indices of ventricular performance in both groups were reduced by 20% compared with their original control values. For this reason, some of the data have also been expressed as percentages of control in each challenge to determine if the depression of these indices was greater in the presence of a narrowed artery (figure 5). The influence of localized ischaemia in a large and small area of the heart on ventricular performance will be described separately.

TABLE II. *Effect of increasing halothane concentration upon regional ventricular function before and during constriction of the left circumflex coronary artery in dogs.* ($n = 5$). *Values are mean ± SEM for the segment supplied by the left anterior descending coronary artery (LAD) and the left circumflex coronary artery (LC). EDL = end diastolic length;* $L_{max}$ *= length from which muscle contracts;* $L_{min}$ *= minimum length during systole; ESL = end-systolic length. Statistical significance symbols refer to paired Student's* t *tests: (a) comparison with pre-constriction or constriction control:* *$P < 0.05$, **$P < 0.01$, ***$P < 0.005$, ****$P < 0.001$. *(b)Comparison with same inspired concentration preconstriction:* †$P < 0.05$; †††$P < 0.005$; ††††$P < 0.001$

| | Before constriction | | | During constriction | | |
|---|---|---|---|---|---|---|
| | Stage | | | Stage | | |
| | 1 | 2 | 3 | 1 | 2 | 3 |
| LAD | | | | | | |
| EDL (mm) | 10.0 | 10.17<br>(0.18) | 10.44<br>(0.19) | 10.03<br>(0.07) | 10.33*<br>(0.15) | 11.01***†<br>(0.14) |
| $L_{max}$ (mm) | 10.08<br>(0.03) | 10.21<br>(0.19) | 10.46<br>(0.20) | 10.06<br>(0.16) | 10.35*<br>(0.16) | 11.01**<br>(0.14) |
| $L_{min}$ (mm) | 8.03<br>(0.22) | 8.53<br>(0.37) | 9.10*<br>(0.22) | 8.29<br>(0.26) | 8.79*<br>(0.34) | 9.35*<br>(0.13) |
| ESL (mm) | 8.05<br>(0.21) | 8.54<br>(0.36) | 9.10*<br>(0.22) | 8.31<br>(0.25) | 8.80*<br>(0.33) | 9.35*<br>(0.13) |
| % Shortening | 20.4<br>(2.0) | 16.6<br>(2.5) | 13.0***<br>(1.5) | 17.8<br>(2.3) | 15.2<br>(2.1) | 15.1†<br>(1.4) |
| LC | | | | | | |
| EDL (mm) | 10.0 | 10.16<br>(0.15) | 10.41*<br>(0.12) | 10.05<br>(0.06) | 10.34<br>(0.16) | 11.08****†<br>(0.10) |
| $L_{max}$ (mm) | 10.08<br>(0.02) | 10.20<br>(0.13) | 10.45*<br>(0.10) | 10.10<br>(0.07) | 10.36<br>(0.16) | 11.09****†<br>(0.10) |
| $L_{min}$ (mm) | 8.74<br>(0.15) | 9.01<br>(0.13) | 9.24<br>(0.07) | 8.78<br>(0.12) | 9.28*<br>(0.17) | 10.61****†††<br>(0.17) |
| ESL (mm) | 8.76<br>(0.16) | 9.02<br>(0.13) | 9.24<br>(0.07) | 8.79<br>(0.12) | 9.30*<br>(0.18) | 10.61****†††<br>(0.17) |
| % Shortening | 13.3<br>(1.6) | 11.6<br>(0.8) | 11.6<br>(0.6) | 13.1<br>(0.7) | 10.4*<br>(0.9) | 4.4****††††<br>(0.9) |

### *LAD stenosis (small area of ischaemic myocardium) (table III and fig. 5)*

There was no significant difference in the magnitude of depression of pressure-based or flow-derived indices of ventricular performance between the two parts of the study at any stage. Thus, at 2% halothane, no haemodynamic variables could be described which were sensitive to ischaemic changes occurring in the LAD segment.

### *LC stenosis (large area of ischaemic myocardium) (table IV and fig. 5)*

All the indices of ventricular performance were more greatly depressed at the greatest tolerated concentration of inspired halothane when compared with the magnitude of depression observed at the same concentration before constriction. These differences were significant for CO and l.v.s.w. In addition, significant differences were seen in l.v.e.d.p., c.p.p. and c.b.f. The profound depression of ventricular performance was reflected by the fact that four of the five animals died after ischaemic depression of contractile function in the LC segment became evident.

### *Interaction between regional and global ventricular performance*

The interaction between regional and global ventricular performance in each group is summarized in

TABLE III. Haemodynamic effects of increasing halothane concentration before and during constriction of the left anterior descending coronary artery in dogs (n = 7). Values are mean ± SEM. Statistical significance symbols refer to paired Student's t tests: (a) comparison with pre-constriction or constriction control: *P < 0.05, **P < 0.01, ***P < 0.005, ****P < 0.001. (b) Comparison with same inspired concentration preconstriction: †P < 0.05, ††P < 0.01, †††P < 0.005

| | Before constriction | | | | During constriction | | | |
|---|---|---|---|---|---|---|---|---|
| | Halothane (%) | | | | Halothane (%) | | | |
| | 0.5 | 1.0 | 1.5 | 2.0 | 0.5 | 1.0 | 1.5 | 2.0 |
| Heart rate<br>(beat min$^{-1}$) | 110<br>(11) | 111<br>(10) | 111<br>(9) | 107<br>(9) | 110<br>(11) | 112<br>(9) | 113<br>(8) | 109<br>(8) |
| MAP<br>(mm Hg) | 78<br>(4) | 68***<br>(4) | 59****<br>(4) | 47****<br>(4) | 81<br>(5) | 72*<br>(4) | 63***<br>(3) | 42***<br>(5) |
| LVEDP<br>(mm Hg) | 5.4<br>(0.7) | 5.9<br>(0.8) | 6.6*<br>(0.8) | 7.4****<br>(0.8) | 6.3<br>(0.6) | 6.4<br>(0.5) | 7.3<br>(0.8) | 8.1<br>(1.0) |
| CPP<br>(mm Hg) | 64<br>(4) | 53***<br>(3) | 44***<br>(4) | 32****<br>(4) | 66<br>(6) | 57*<br>(4) | 47***<br>(4) | 27***<br>(5) |
| LV $dP/dT_{max}$<br>(mm Hg s$^{-1}$) | 1360<br>(70) | 1130***<br>(50) | 910****<br>(45) | 660****<br>(55) | 1255<br>(100) | 1035***<br>(80) | 885****<br>(70) | 580****<br>(65) |
| Ao. blood acceln<br>(ml s$^{-2}$) | 5490<br>(410) | 4370****<br>(360) | 3385****<br>(255) | 2290****<br>(225) | 4215†<br>(350) | 3630***†<br>(290) | 2970****†<br>(260) | 1825****<br>(275) |
| Cardiac output<br>(ml min$^{-1}$) | 2345<br>(115) | 2130<br>(90) | 1935*<br>(95) | 1410***<br>(140) | 1840††<br>(115) | 1765††<br>(110) | 1620*†††<br>(120) | 1080***†<br>(225) |
| LVSW<br>(mJ) | 233<br>(21) | 182**<br>(22) | 145***<br>(19) | 89***<br>(17) | 190<br>(22) | 156***<br>(16) | 125****<br>(16) | 65****†<br>(20) |
| SVR<br>(mm Hg litre$^{-1}$ s) | 2025<br>(135) | 1935<br>(135) | 1845<br>(180) | 2070<br>(180) | 2745†<br>(315) | 2565†<br>(225) | 2385††<br>(225) | 2970<br>(585) |

figures 2 and 3. Depression of shortening in both segments under study is shown in conjunction with changes in c.p.p. and CO. Figure 2 shows that, at a time when performance in the LAD was severely impaired, ventricular performance was maintained. This is in marked contrast to the situation when the LC segment became impaired (fig. 3) and there were significant reductions in global haemodynamics, despite an improvement in shortening in the control segment.

## DISCUSSION

Anaesthesia for patients with ischaemic heart disease is an increasingly important clinical problem. The experimental studies which have recognized this by examining the interaction between anaesthesia and the ischaemic myocardium have utilized models with coronary artery occlusion (Bland and Lowenstein, 1976; Davis et al., 1979; Smith, Rogers and Thorburn, 1980). This approach may have limited clinical relevance, since patients suffering from recent myocardial infarction make up a small proportion of those with ischaemic heart disease who present for surgery. This study has chosen to constrict vessels critically in an attempt to mimic non-occlusive coronary artery disease. The constriction applied was such that resting flow was decreased by a small amount, but the coronary flow reserve in the vasculature distal to the stenosis was abolished. In group 1 (LAD stenosis), constriction was judged to be critical if hypoxia led to a differential response between the myocardium supplied by a narrowed artery and that with an undisturbed blood supply. The test was accompanied by some deterioration of haemodynamics at a global and a regional level. For this reason, coronary blood flow was measured in group 2 (LC stenosis) so that critical constriction could be defined as the degree of narrowing which abolished 95% of the hyperaemic response to a 10-s occlusion of the vessel (Elzinga and Skinner, 1975). In applying the constriction in group 2, coronary blood flow was reduced by 15%.

TABLE IV. *Haemodynamic effects of increasing halothane concentration before and during constriction of the left circumflex coronary artery in dogs ($n = 5$). Values are mean ± SEM. Statistical significance symbols refer to paired Student's t tests: (a) comparison with preconstriction or constriction control:* *$P < 0.05$, **$P < 0.01$, ***$P < 0.005$, ****$P < 0.001$. *(b) Comparison with same inspired concentration preconstriction:* †$P < 0.05$, ††$P < 0.01$, †††$P < 0.005$, ††††$P < 0.001$

| | Before constriction | | | During constriction | | |
|---|---|---|---|---|---|---|
| | Stage | | | Stage | | |
| | 1 | 2 | 3 | 1 | 2 | 3 |
| Heart rate | 127 | 127 | 120**** | 127 | 128 | 125 |
| (beat min$^{-1}$) | (11) | (9) | (10) | (8) | (7) | (7) |
| MAP | 80 | 61* | 43**** | 79 | 56** | 30**** |
| (mm Hg) | (1) | (5) | (4) | (3) | (7) | (3) |
| LVEDP | 5.0 | 6.0 | 7.6* | 5.8 | 7.6* | 10.8****† |
| (mm Hg) | (0.9) | (1.3) | (1.2) | (0.4) | (0.7) | (0.4) |
| CPP | 67 | 47* | 29**** | 65 | 42** | 14****† |
| (mm Hg) | (2) | (5) | (4) | (3) | (7) | (3) |
| LV $dP/dt_{max}$ | 1430 | 980* | 670*** | 1270† | 860** | 450****† |
| (mm Hg s$^{-1}$) | (80) | (70) | (60) | (30) | (70) | (40) |
| Ao. blood acceln | 3910 | 2480 | 1490** | 2910† | 1820*††† | 760**† |
| (ml s$^{-2}$) | (570) | (220) | (150) | (390) | (260) | (160) |
| Cardiac output | 1860 | 1425 | 900*** | 1500††† | 1010*††† | 375****†††† |
| (ml min$^{-1}$) | (165) | (170) | (75) | (135) | (150) | (195) |
| LVSW | 162 | 97* | 44*** | 126† | 63**† | 13***†† |
| (mJ) | (23) | (25) | (6) | (16) | (17) | (4) |
| SVR | 2700 | 2655 | 2925 | 3330† | 3465 | 7560 |
| (mm Hg litre$^{-1}$ s) | (315) | (315) | (405) | (450) | (495) | (3105) |
| Coronary blood flow | 42.6 | 32.5* | 26.3**** | 30.6†††† | 23.1***†††† | 7.4***††† |
| (ml min$^{-1}$ per 100 g) | (3.0) | (3.9) | (2.2) | (2.4) | (3.0) | (1.1) |

It must be noted that, although the test for abolition of autoregulation differed in the two groups, the manner in which the constriction was applied was the same, that is the artery was constricted to a point where any further narrowing led to impairment of shortening in the myocardium supplied. The inability of the vascular bed distal to the constriction to autoregulate is comparable to angina pectoris in which resting flow is adequate for the basal oxygen demand, but is unable to increase in response to stress.

It is now recognized that, in the presence of coronary artery disease, an intervention may produce divergent responses in different segments of the heart with no overall change in global performance (Forrester et al., 1974). Dissociation between regional and global myocardial performance can be recognized if sensitive indices of regional myocardial performance are used. The measurement of regional myocardial shortening was used since changes in shortening pattern at this level have been shown to be very sensitive to ischaemia (Smith, Kent and Epstein, 1978; Miller et al., 1979). The contraction pattern obtained by implanting crystals in the minor axis of the heart does not simply alternate between shortening during ejection and lengthening during diastole, but is complicated by subsidiary changes superimposed on this pattern. It was for this reason that four points during systole were routinely identified (i.e. EDL, $L_{max}$, $L_{min}$, ESL). The changes of length, which are observed during the isovolumic phase, are likely to reflect a rearrangement of the ventricle at this time. A greater interval of shortening was observed in the LAD segment than in the LC segment. This lends support to previous observations that the apex of the heart is more dynamic than the base (LeWinter et al., 1975). It was decided to express the regional length data as

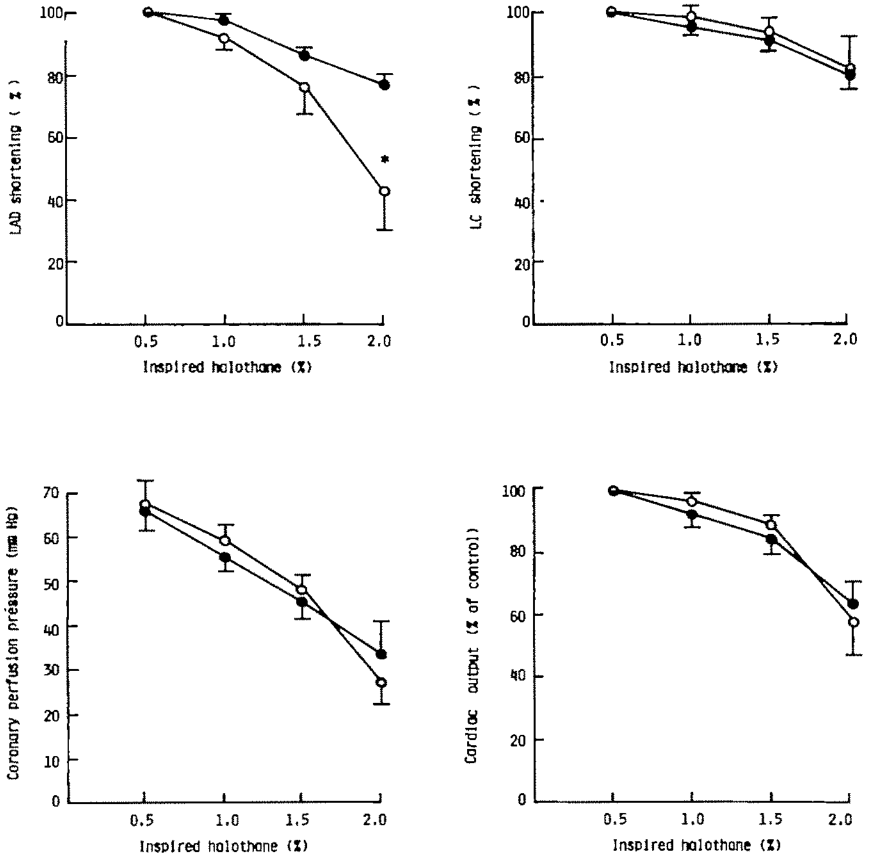

FIG. 2. The effect of increasing inspired halothane on regional and global haemodynamics before and during constriction of the LAD coronary artery is illustrated. Before constriction, shortening in both segments under study, coronary perfusion pressure (c.p.p.) and cardiac output (CO) were all reduced in a dose-dependent fashion. During constriction, the LAD segment shortened less at each inspired concentration than before constriction (upper left hand panel) whilst shortening in the LC segment was maintained (upper right hand panel). In addition, the impaired shortening in the LAD segment was not reflected in c.p.p. (lower left hand panel) or CO (lower right hand panel). All the data are expressed as mean ± SEM (● = preconstriction; ○ = during constriction; $^*P < 0.05$).

an interval of shortening since alternative measurements (e.g. velocity of segmental shortening) have not been shown to have any advantages as indices of regional performance.

The influence of halothane on the performance of normal myocardium can be assessed if the data from the first halothane challenge in each group are considered. The dose-dependent depression of all indices of global myocardial performance demonstrates the negative inotropic action of halothane and agrees well with earlier work (Prys-Roberts et al., 1972; Vatner and Smith, 1974; Merin, Verdouw and de Jong, 1977; Sonntag et al., 1978, 1979). The depression was accompanied by a dose-dependent reduction in c.b.f. (group 2) which reflects the decreased metabolic demand of the myocardium (Merin, Kumazawa and Luka, 1976).

Segmental shortening is very sensitive to changes in preload, afterload and contractility. An increase in preload or a decrease in afterload is accompanied by an increase in shortening and *vice versa*. Changes in contractility are followed by directionally similar changes in shortening (Bugge-Asperheim and Kiil, 1973). Halothane caused a dose-dependent reduction in shortening which must reflect a depression of regional contractility, since left ventricular filling (preload) was increased and systemic vascular resistance (afterload) unchanged.

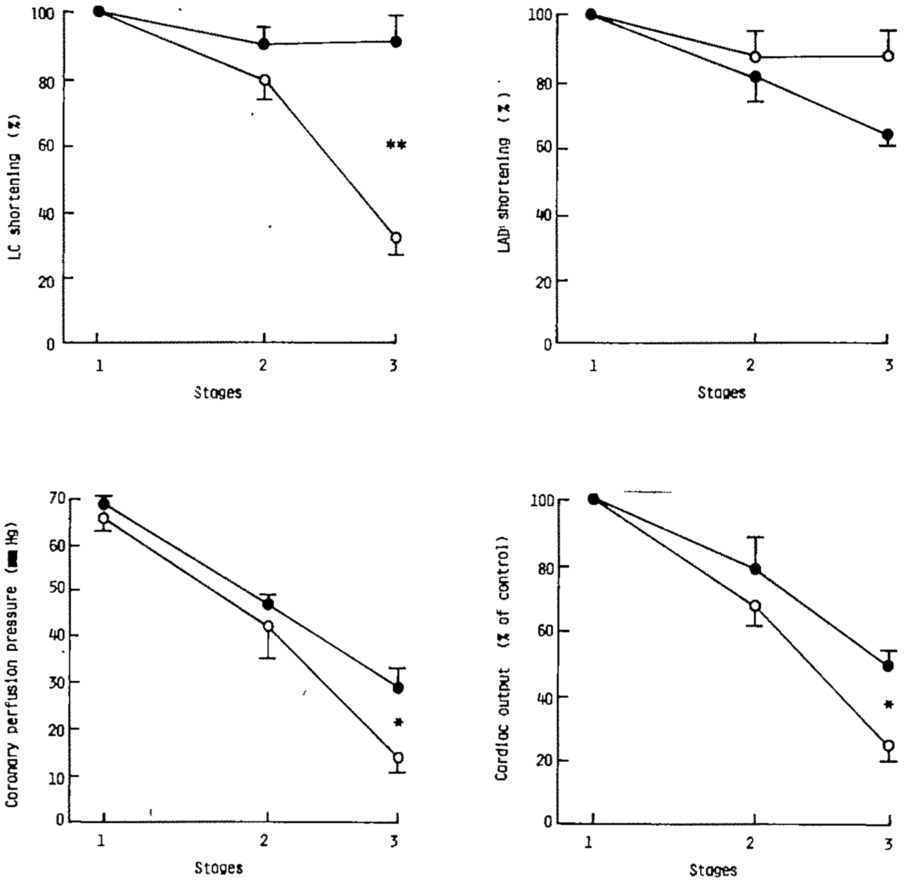

FIG. 3. The effect of increasing inspired halothane concentration on regional and global haemodynamics before and during constriction of the LC coronary artery is illustrated. Before constriction, shortening in both segments, coronary perfusion pressure (c.p.p.) and cardiac output (CO) were reduced in a dose-dependent fashion. During constriction, shortening in the LC segment was less at each inspired concentration than at the same stages before constriction (upper left hand panel) and this effect was highly significant at stage 3. In contrast, shortening in the LAD segment was less depressed (upper right hand panel). However, the impaired shortening in the LC was reflected in a significantly greater depression of c.p.p. (lower left hand panel) and CO (lower right hand panel). All the data are mean ± SEM (● = preconstriction; ○ = during constriction; $*P<0.05$; $**P<0.01$).

This study confirms previous work from this laboratory by demonstrating that halothane causes severe depression of contractile function in an area of myocardium supplied by a stenosed artery (figs 2 and 3). The exaggerated depression may have been mediated by an enhanced depressant effect of halothane on myocardium with a limited blood supply or by the development of ischaemia. The latter is favoured for two reasons:

(i) in both groups abnormal contraction patterns compatible with ischaemia and of varying severity were observed;

(ii) in group 2 there was a sharp reduction in coronary blood flow accompanying the loss of contractile function (fig. 6).

Wall motion in severe ischaemia is characterized by the segment lengthening during systole and shortening in early diastole (post-systolic shortening, PSS). It has been suggested (Tyberg and Parmley, 1978) that paradoxical wall motion reflects a discrepancy in tension development between the ischaemic myocardium and the neighbouring myocardium. The rate of tension development in the ischaemic muscle is less than in the normal muscle so that the ischaemic muscle is stretched (systolic lengthening) and then shortens by elastic

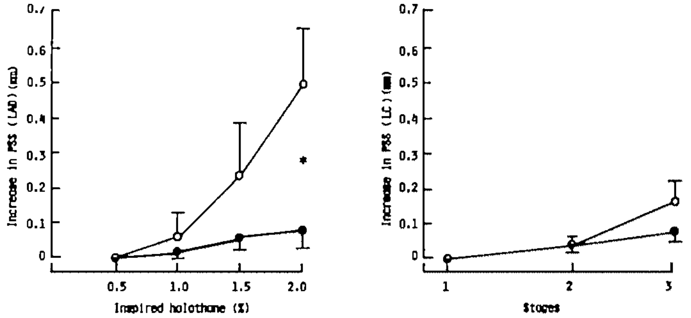

FIG. 4. The effect of increasing inspired halothane concentration upon post-systolic shortening (PSS) in the LAD and LC segments before and during constriction of the nutrient artery is illustrated. When the LAD artery was constricted the degree of PSS observed was greater than that noted before constriction. This difference became significant at 2% (*$P < 0.05$). In contrast, the degree of PSS observed in the LC segment was not significantly greater during constriction than before. All the data are expressed as mean ± SEM for those dogs in which ischaemia developed.

recoil (PSS). The degree of dysfunction which is observed as ischaemia progresses, will depend on the magnitude of this discrepancy in tension development. The interaction between normal and ischaemic myocardium to produce abnormal wall motion is further highlighted in this study. The degree of dysfunction was greater in the ischaemic segment of group 1 than that of group 2. This is shown in figure 4, where the increase in PSS is seen to be much greater in group 1 than in group 2. This is a reflection of the different masses of ischaemic muscle involved. Approximately 50% of the LV free wall was supplied by the stenosed artery in group 2. Thus, the non-ischaemic muscle was unable to develop sufficient tension to stretch such a large mass of ischaemic muscle. For this reason PSS in the ischaemic segment was not as pronounced despite the severe reduction in shortening. The mass of muscle supplied in group 1 was not measured but subsequent work with the model has shown that approximately 25% is supplied by the LAD distal to the second diagonal branch (unpublished data). Thus, the ischaemic muscle was easily stretched by the non-ischaemic muscle with the result that PSS was more pronounced in group 1 than in group 2. These data demonstrate that PSS alone cannot be used as an indicator of ischaemia.

The mechanism underlying the onset of ischaemia can be described if the relationship between myocardial oxygen supply and demand is considered. The primary determinants of coronary blood flow (oxygen supply) are: (i) coronary vascular resistance (CVR), (ii) coronary perfusion pressure (c.p.p.) and (iii) extra-vascular compression. The two definitions of critical constriction used in this study eliminated changes in CVR distal to the stenosis as a determinant of flow. Thus, after constriction, c.p.p. was largely responsible for flow in the vessel under study. The oxygen balance in the segment supplied by the narrowed artery was precarious since the coronary vasculature distal to the stenosis had lost its ability to autoregulate. Halothane has a profound influence on both oxygen supply and demand after critical constriction. Oxygen demand is decreased by the reduction in systolic wall tension and myocardial contractility, although this beneficial effect is partially offset by an increase in diastolic wall tension, which increases oxygen demand. However, the net reduction in oxygen demand is achieved at the expense of c.p.p., which is decreased in a dose-dependent fashion. Ischaemia developed because c.p.p. (and, therefore, c.b.f.) decreased faster than myocardial oxygen demand and a point was reached at which the oxygen balance could no longer support normal regional myocardial function. In both studies, there was a sharp cut-off point after which shortening deteriorated rapidly. The cut-off point represents the last stage at which oxygen supply was sufficient for oxygen demand and, therefore, corresponds to the second point in the analysis of the data in group 2.

The foregoing analysis would suggest that changes in c.p.p. should correlate with changes of function in muscle supplied by a narrowed artery. However, c.p.p. can only be correlated with a severe reduction of segmental shortening if there is an equivalent depression of global performance as occurred in group 2. C.p.p. has usually been calcu-

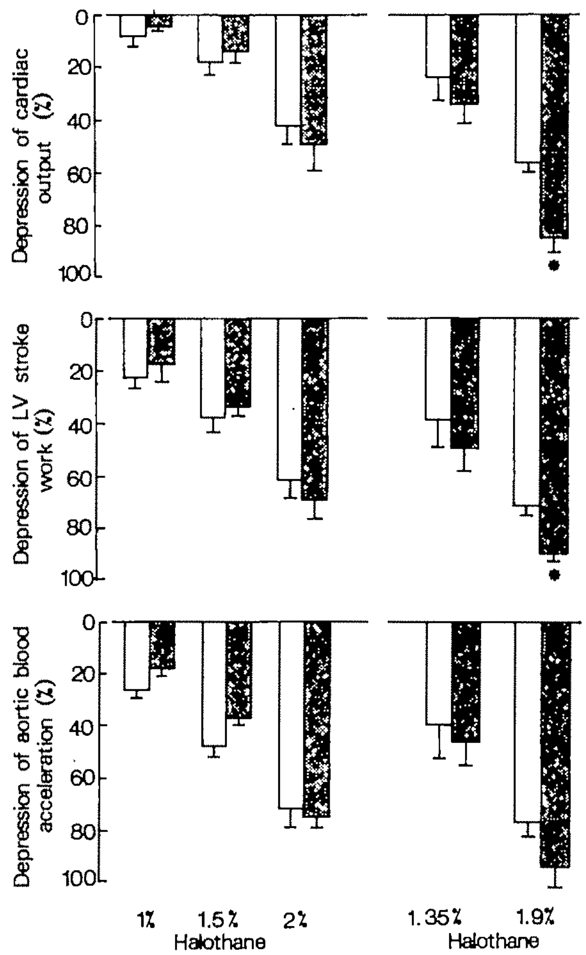

FIG. 5. Influence of halothane on global cardiac function with and without critical constriction of left anterior descending coronary artery (group 1) (left side) or left circumflex coronary artery (right side). The open bars indicate the percentage reduction from control before constriction and the solid bars represent the depression during constriction. There was no significant difference in the magnitude of depression of global haemodynamics between the two parts of the experiment in group 1 (LAD stenosis). However, in group 2 (LC stenosis), global myocardial performance was more greatly depressed at a time when shortening in the LC segment was severely impaired (stage 3). The data are expressed as mean ± SEM ($^*P<0.05$).

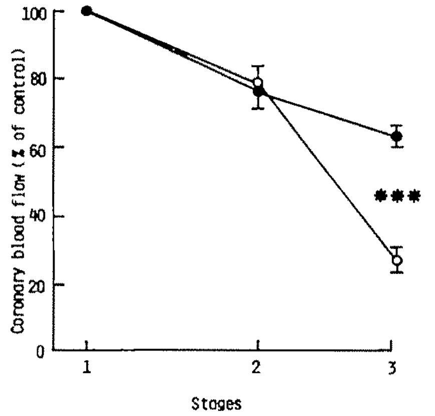

FIG. 6. The effect of increasing inspired halothane concentration on coronary blood flow (expressed as percentage reduction from control) is illustrated. Before constriction, c.b.f. decreased in a dose-dependent fashion. During constriction, c.b.f. decreased markedly between stages 2 and 3 at a time when shortening in the LC segment deteriorated rapidly (● = preconstriction; ○ = during constriction; $^{***}P<0.005$).

lated as the difference between the driving pressure for flow (d.a.p.) and the back pressure opposing flow (l.v.e.d.p.). However, the use of d.a.p. and l.v.e.d.p. are both subject to criticism in the context of this study. In the presence of a stenosis, the pressure distal to the stenosis (distal coronary pressure) is the driving pressure for flow and is less than d.a.p. although the magnitude of this difference declines at lower flow rates across the stenosis (Young et al., 1977). The assumption that l.v.e.d.p. is equal to the back pressure opposing flow has been questioned by recent work considering the critical closing pressure as being the more important determinant of the back pressure (Bellamy, 1980; Verrier et al., 1980). The critical closing pressure is greater than l.v.e.d.p., and the distal coronary pressure is less than d.a.p. so that the classical calculation of c.p.p. is an overestimate of the real perfusion pressure in vasculature distal to a stenosis. These considerations also suggest that d.a.p. can only be a crude indicator of the adequacy of coronary perfusion in the patient with ischaemic heart disease undergoing anaesthesia.

An ischaemic segment cannot contribute to the pumping function of the heart since the majority of shortening occurs after valve closure. For this reason, it was hoped that indices of ventricular performance derived from the measurement of aortic flow would be more sensitive in the detection of regional myocardial ischaemia, in particular ischaemia confined to a small area of the LV wall. However, figure 5 shows that when a small area of the myocardium became ischaemic (group 1) ventricular performance was not severely compromised and the ischaemia remained undetected. Thus, flow-derived indices are no more sensitive in detecting ischaemia in a small area of the heart than are those based on pressure measurements. This is in marked contrast to the influence of a large area of ischaemic myocardium as was present in group 2 (fig. 5). Global performance declined in parallel with shortening in the LC segment and was so severely depressed that four of the five animals died because of pump failure. In group 1, incomplete recovery of regional shortening was noted in three of the five segments which became ischaemic. This was despite a relatively short duration of ischaemia. This suggests that a more prolonged episode of ischaemia may lead to permanent damage of the LV wall.

The preservation of global ventricular performance when a small area of myocardium became ischaemic may reflect compensatory increases in shortening in areas of non-ischaemic myocardium. Increased contraction has been described in response to the dyskinesia produced by acute coronary arterial occlusion (Theroux et al., 1974). Increased shortening was observed in the control segment when dysfunction became apparent in the ischaemic segment in two dogs in group 1 and in all dogs of group 2. The evolution of a compensatory increase in shortening may depend on the mass of ischaemic muscle and the proximity of the control segment under study to the ischaemic muscle. It is not possible from this data to determine whether the increased shortening was mediated by an active or a passive mechanism. For example, the increased shortening in group 2 occurred at a time when ventricular filling was increased, which would favour a passive mechanism. However, such changes in load on the myocardium were not seen in group 1 at the time of increased shortening, which would suggest an active component to the mechanism. This problem will only be solved when a more refined index of regional contractility than systolic shortening is found, since this will allow active and passive mechanisms to be distinguished.

This study has demonstrated that halothane causes contraction abnormalities in myocardium supplied by a critically narrowed artery and that this may have a profound influence on global performance if a large area of the LV wall is involved. Any extrapolation of these laboratory findings to clinical practice should be made with great caution. However, these experimental findings offer an explanation for some clinical observations. Anaesthetists titrate the concentration of halothane to provide circulatory stability in the knowledge that some patients with ischaemic heart disease tolerate lower concentrations than do others. Patients with widespread ischaemic heart disease will have a large area of myocardium which is potentially ischaemic. If ischaemia evolves as a result of decreased perfusion, a precipitous hypotension may develop as was observed in group 2 of this study. In clinical practice this can often be remedied by the prompt reduction in anaesthetic concentration. However, if the coronary vascular disease of the patient is localized, a small area of myocardium may become severely compromised without this being evident clinically. Prolonged ischaemia in this situation may lead to permanent damage of the ventricular wall. This may explain why cardiac complications sometimes develop in patients suffering from ischaemic heart disease in the early postoperative period despite an apparently stable cardiovascular state during surgery.

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## REFERENCES

Bellamy, R. F. (1980). Calculation of coronary vascular resistance. *Cardiovasc. Res.*, 14, 261.

Bland, J. H. L., and Lowenstein, E. (1976). Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. *Anesthesiology*, 45, 287.

Brown, B. R., and Crout, J. R. (1971). A comparative study of the effects of five general anesthetics on myocardial contractility: I. Isometric conditions. *Anesthesiology*, 34, 236.

Bugge-Asperheim, B., and Kiil, F. (1973). Preload, contractility and afterload as determinants of stroke volume during elevation of aortic blood pressure in dogs. *Cardiovasc. Res.*, 7, 528.

Davis, R. F., DeBoer, L. W. V., Rude, R. W., Lowenstein, E., and Maroko, P. R. (1979). Beneficial effect of halothane anesthesia on myocardial infarction size in dogs. *Crit. Care Med.*, 7, 134.

Eger, E. I., Smith, N. T., Stoetling, R. K., Cullen, D. J., Kadis, L. B., and Witcher, C. E. (1970). Cardiovascular effects of halothane in man. *Anesthesiology*, 32, 396.

Elzinga, W. E., and Skinner, D. B. (1975). Hemodynamic characteristics of critical stenosis in canine coronary arteries. *J. Thorac. Cardiovasc. Surg.*, 69, 217.

Forrester, J. S., Tyberg, J. V., Wyatt, H. L., Goldner, S., and Parmley, W. W. (1974). Pressure length loop: a new method for simultaneous measurement of segmental and total cardiac function. *J. Appl. Physiol.*, 37, 771.

Franklin, D. L., Kemper, W. S., Patrick, T., and McKown, D.

(1973). Technique for continuous measurement of regional myocardial segment dimensions in chronic animal preparations. *Fed. Proc.*, 32, 343.

Gersh, B. J., Hahn, C. E. W., and Prys-Roberts, C. (1971). Physical criteria for measurement of left ventricular pressure and its first derivative. *Cardiovasc. Res.*, 55, 32.

Goldberg, A. H., and Ullrick, W. C. (1967). Effects of halothane on isometric contractions of isolated heart muscle. *Anesthesiology*, 28, 838.

Hagl, S., Heimisch, W., Meisner, H., Erben, R., Baum, M., and Mendler, N. (1977). The effect of hemodilution on regional myocardial function in the presence of coronary stenosis. *Basic Res. Cardiol.*, 72, 344.

LeWinter, M. M., Kent, R. S., Kroener, J. M., Carew, T. E., and Covell, J. W. (1975). Regional differences in myocardial performance in the left ventricle of the dog. *Cir. Res.*, 37, 191.

Lowenstein, E., Foëx, P., Francis, C. M., Davies, W. L., Yusuf, S., and Ryder, W. A. (1981). Regional ischemic ventricular dysfunction in myocardium supplied by a narrowed artery with increasing halothane concentration in the dog. *Anesthesiology*, 55, 100.

McDonald, D. A. (1974). *Blood Flow in Arteries*, 2nd edn. London: Edward Arnold Ltd.

Merin, R. G. (1980). Is anesthesia beneficial for the ischemic heart? *Anesthesiology*, 53, 439.

—— Kumazawa, K., and Luka, N. L. (1976). Myocardial function and metabolism in the conscious dog and during halothane anesthesia. *Anesthesiology*, 44, 402.

—— Verdouw, P. D., and de Jong, J. W. (1977). Dose-dependent depression of cardiac function and metabolism by halothane in swine (*Sus scrofa*). *Anesthesiology*, 46, 417.

Miller, M. M., Thorvaldson, J., Ilebekk, A., and Lekven, J. (1979). Myocardial ischemia, relationship between local flow, function and S–T segment elevation. *Eur. J. Cardiol.*, 10, 7.

Prys-Roberts, C., Gersh, B. J., Baker, A. B., and Reuben, S.R. (1972). The effects of halothane on the interactions between myocardial contractility, aortic impedance and left ventricular performance. I. Theoretical considerations and results. *Br. J. Anaesth.*, 44, 634.

—— Lloyd, J. W., Fisher, A., Kerr, J. H., and Patterson, T. J. J. (1974). Deliberate profound hypotension induced with halothane. Studies of haemodynamics and pulmonary gas exchange. *Br. J. Anaesth.*, 46, 105.

Roberts, J. G., Foëx, P., Clarke, T. N. S., Prys-Roberts, C., and Bennett, M. J. (1976). Haemodynamic interactions of high-dose propranolol pre-treatment and anaesthesia in the dog. I. Halothane dose–response studies. *Br. J. Anaesth.*, 48, 315.

Smith, G., Rogers, K., and Thorburn, J. (1980). Halothane improves the balance of oxygen supply to demand in acute experimental myocardial ischaemia. *Br. J. Anaesth.*, 52, 577.

Smith, H. J., and Kent, K. M., and Epstein, S. E. (1978). Relationship between regional contractile function and S–T segment elevation after experimental coronary artery occlusion in the dog. *Cardiovasc. Res.*, 12, 444.

Sonntag, H., Donath, U., Hillebrand, W., Merin, R.G., and Radke, J. (1978). Left ventricular function in conscious man and during halothane anesthesia. *Anesthesiolgy*, 48, 320.

—— Merin, R. G., Donath, U., Radke, J., and Schenk, H. D. (1979). Myocardial metabolism and oxygenation in man awake and during halothane anesthesia. *Anesthesiology*, 51, 204.

Sugai, N., Shimosato, S., and Etsten, B. E. (1968). Effects of halothane on force–velocity relations and dynamic stiffness of isolated heart muscle. *Anesthesiology*, 29, 267.

Theroux, P., Franklin, D., Ross, J., and Kemper, W. S. (1974). Regional myocardial function during acute coronary artery occlusion and its modification by pharmacologic agents in the dog. *Circ. Res.*, 35, 896.

Tyberg, J. V., and Parmley, W. W. (1978). Mechanics of myocardial ischaemia. *Adv. Cardiol.*, 23, 40.

Vatner, S. F., and Smith, N. T. (1974). Effects of halothane on left ventricular function and distribution of regional blood flow in dogs and primates. *Circ. Res.*, 34, 155.

Verrier, E. D., Edelist, G., Consigny, P. M., Robinson, S., and Hoffman, J. I. E. (1980). Greater coronary vascular reserve in dogs anesthetized with halothane. *Anesthesiology*, 53, 445.

Young, D. F., Cholvin, N. R. , Kirkeeide, R. L., and Roth, A. C. (1977). Hemodynamics of arterial stenosis at elevated flow rates. *Circ. Res.*, 41, 99.

## INTERACTION ENTRE L'ISCHEMIE MYOCARDIQUE REGIONALE ET LA PERFORMANCE VENTRICULAIRE GAUCHE AU COURS DE L'ANESTHESIE A L'HALOTHANE

### RESUME

L'effet de l'halothane sur la performance d'un myocarde irrigué par une artère coronaire sténosée a été étudié pour tenter de préciser l'influence de l'halothane sur des coeurs souffrant de coronaropathies non obstructives. L'étude a été divisée en deux parties: dans la première, la coronaire inter-ventriculaire antérieure (IVA) était partiellement clampée en aval de la deuxième collatérale et dans la deuxième, l'artère circomflexe était partiellement clampée tout près de son origine. Dans les deux cas, le myocarde était soumis à des augmentations par paliers de l'halothane inspiré avant et après le clampage du vaisseau étudié. L'approfondissement de l'anesthésie à l'halothane conduit à une dépression dose-dépendante de la performance myocardique régionale et globale avant clampage. Après clampage, des modifications ischémiques des courbes de contractilité du myocarde ayant un apport sanguin réduit étaient notées. Si l'ischémie était limitée à une petite zone myocardique (sténose de l'IVA) il n'y avait pas de détérioration significative de la performance globale du VG. Cependant une ischémie étendue (sténose circomflexe) conduirait à une défaillance cardiaque irréversible chez quatre des cinq animaux étudiés.

## DIE WECHSELWIRKUNG ZWISCHEN REGIONALER MYOKARDIALER ISCHÄMIE UND DER LEISTUNG DES LINKEN VENTRIKELS BEI DER HALOTHANNARKOSE

### ZUSAMMENFASSUNG

Die Wirkung des Halothans auf die Leistung des von einer verengten Koronararterie versorgten Myokards wurde in einer Studie untersucht, um die Wirkung des Halothans auf Herzen mit nicht obstruktiver Koronararterienerkrankung beurteilen zu können. Die Studie wurde in zwei Abschnitte unterteilt: Beim ersten wurde die A. anterior descendens (LAD) hinter ihrer 2. diagonalen Abzweigung verengt. Beim 2. Abschnitt wurde die A. circumflexans sinistra (LC) nahe an ihrem Ursprung eingeengt. Beide Male wurde das Myokard schrittweise höheren Anteilen von Halothan im Inspirationsgemisch ausgesetzt, und zwar vor und nach kritischer Einengung des Gefäßes. Tiefere Halothan-

zufuhr führte zu dosisabhängiger Herabsetzung der regionalen und globalen myokardialen Leistung vor der kritischen Einengung. Nach der Konstriktion waren ischämische Veränderungen des Kontraktionsmusters des Myokardanteils zu bemerken, dessen Blutzufuhr gedrosselt war. Wenn die Ischämie auf ein kleines Gebiet des Herzens begrenzt waar (LAD-Stenose), gab es keine signifikante Störung der globalen Leistung des linken Ventrikels. Jedoch führte eine ausgedehnte Ischämie (LC-Stenose) zu irreversiblem Herzversagen bei vier der funf untersuchten Tiere.

## INTERACCION ENTRE LA ISQUEMIA REGIONAL DEL MIOCARDIO Y EL FUNCIONAMIENTO DEL VENTRICULO IZQUIERDO BAJO ANESTESIA POR HALOTANO

### SUMARIO

Se ha evaluado el efecto del halotano en el funcionamiento del miocardio, suministrándolo a través de una delgada arteria coronaria, en un intento de examinar su influencia en corazones con enfermedades coronarias no oclusivas. El estudio comprendió dos partes: en la primera de éstas, la arteria coronaria anterior, descendiente e izquierda, se constriñó más allá de su segunda ramificación diagonal y en la segunda el circunflejo izquierdo se constriñó hasta cerca de su origen. En ambos casos el miocardio quedó expuesto a incrementos discontinuos del halotano inspirado, antes y después de la reducción crítica del vaso bajo estudio. El hacer más profunda la anestesia por halotano condujo a una depresión del funcionamiento miocardial global y regional que fue dependiente de la dosis, lo que tuvo lugar antes de la reducción crítica. Después de la reducción se apreciaron cambios isquémicos en la estructura de la contracción que se había obtenido para el miocardio junto con un suministro de sangre limitado. Cuando la isquemia se redujo a una pequeña zona del corazón (estenosis del lado ezquierdo anterior descendente), no se produjo deteriorización significativa del funcionamiento global del ventrículo izquierdo. Sin embargo, la isquemia distribuida (estenosis del circunflejo izquierdo) condujo a ataques cardiacos irreversibles en cuatro de los cinco animales estudiados.

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# EFFECT OF HALOTHANE ON CALCIUM TRANSPORT IN ISOLATED HEPATIC ENDOPLASMIC RETICULUM

J. R. ZUCKER, E. M. DIAMOND AND M. C. BERMAN

SUMMARY

The effects of halothane on calcium transport by microsomes prepared from rat liver have been studied. Pre-incubation of microsomal suspensions in the presence of halothane, irreversibly inactivated ATP-dependent calcium transport. The effects were dose-dependent and time-dependent and were potentiated by acid conditions (pH 6.0). The observed *in vitro* effects of halothane may, by increasing cytosolic concentrations of calcium, be relevant to the hepatotoxic effects of halothane.

Halothane is regarded as a safe general anaesthetic agent, but occasionally malignant hyperthermia and acute hepatic dysfunction are associated with its use.

The case for a relationship between hepatitis and halothane exposure seems to have been proven (Sherlock, 1978). Many mechanisms have been postulated, including direct hepatotoxicity of halothane or one of its reactive metabolized products (Brown and Sipes, 1977). Another proposed mechanism is an allergic or immune response (Vergani et al., 1980), but the exact mechanism is obscure, and in individual cases halothane hepatitis is still a diagnosis of exclusion.

In malignant hyperthermia the acute changes are compatible with the proposed role of an increase in cytosolic calcium concentration (Berman et al., 1970). One mechanism postulated is that halothane uncouples calcium transport from ATP hydrolysis in the sarcoplasmic reticulum of skeletal muscle. This triggering effect of halothane may be perpetuated by a vicious cycle of events resulting from irreversible acid-induced inactivation of calcium transport in the sarcoplasmic reticulum of susceptible individuals (Diamond and Berman, 1980).

In the liver, maintenance of low intracellular calcium concentration is necessary for normal hepatic function. The endoplasmic reticulum of liver actively sequesters calcium to maintain micromolar cytoplasmic concentrations against a concentration gradient (Becker, Fiskum and Lehninger, 1980). In the present study we investigated the effect of halothane on this process. *In vitro*, ATP-dependent uptake of calcium by rat liver microsomes was measured by assaying calcium-45 sequestered into the microsomes, and the effect of halothane on this process was studied.

This molecular effect of halothane on calcium transport may be common to many of the observed events following exposure to halothane and may provide some of the answers to the question of halothane hepatitis.

## MATERIALS AND METHODS

Healthy adult male Sprague–Dawley rats were starved overnight, stunned by sharp blows to the back of their necks and decapitated. The livers were removed and immediately placed into ice-cold homogenizing medium containing sucrose 250 mmol litre$^{-1}$, N-2-hydroxyethylpiperazine-N′-2-ethanesulphonic acid (HEPES) 2.5 mmol litre$^{-1}$, ethyleneglycol-bis ($\beta$-aminoethyl ether) N, N′-tetra-acetic acid (EGTA) 0.5 mmol litre$^{-1}$. All further manipulations were carried out at 0–4 °C. Livers were washed, sliced with scissors, passed through a Harvard tissue press, and homogenized in a glass homogenizer fitted with a Teflon pestle for five or six passes. The suspension was centrifuged at 3000 × *g* for 10 min and the supernatant centrifuged for 25 min at 17 000 × *g* in a refrigerated centrifuge. The supernatant was then centrifuged at 100 000 × *g* for 60 min and the pellet washed and resuspended carefully in sucrose 250 mmol litre$^{-1}$, HEPES 2.5 mmol litre$^{-1}$ to give a final protein concentration of 5–10 mg ml$^{-1}$. Mitochondrial contamin-

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ation, as determined by the succinate dehydrogenase activity method of Estabrook (1967) was less than 2%. Microsomal cytochrome *c* reductase activity, determined by the method of Mackler (1967) was 0.35 μmol min$^{-1}$ mg$^{-1}$ of protein, in agreement with previous quoted values.

Calcium uptake by microsomes was measured in the medium described by Moore and others (1975). This consisted of potassium chloride 100 mmol litre$^{-1}$, histidine–imidazole buffer 30 mmol litre$^{-1}$, pH 6.8, magnesium chloride 5 mmol litre$^{-1}$, potassium oxalate 5 mmol litre$^{-1}$, calcium chloride 40 μmol litre$^{-1}$ and $^{45}CaCl_2$ 0.1 μCi ml$^{-1}$. The reaction at 37 °C was initiated by the addition of ATP 5 mmol litre$^{-1}$ to the test-tube containing microsomes and uptake medium. Non-specific binding of calcium was determined in the absence of ATP. At fixed time intervals aliquots were filtered onto millipore filters (0.45-μm pore size), washed and the residual calcium-45 radioactivity determined in a Beckman LS233 scintillation spectrometer after dissolving the filters in 4 ml of Instagel (Packard Instruments).

A total of 100 rat livers was used over a period of 6 months. Each freshly prepared microsomal suspension was tested and discarded if contaminated or partially denatured during preparation. The fresh microsomes were used immediately and all experiments were completed within 4 h of preparation. The calcium uptake determined during testing was used as the baseline for the halothane inactivation experiments. Nonspecific binding of calcium was determined with every manipulation of each batch of microsomes.

The effect of halothane on the ATP-dependent uptake of calcium ions was investigated by pre-incubating the microsomes *in vitro* in the absence of calcium chloride or calcium-45 in media containing varying halothane concentrations as previously described by Diamond and Berman (1980). Timed pre-incubations were performed at 37 °C in a narrow-gauge, thick-walled glass coil with thermostat to prevent volatilization of halothane. Samples (50 μlitre) were delivered from the coil at timed intervals directly into uptake medium (425 μlitre) kept at 0 °C. Under these conditions residual calcium transport remained constant until assay (within 60 min). All calcium uptake studies were performed at 37 °C and were initiated by addition of ATP 5 mmol litre$^{-1}$ (25 μlitre).

All experiments were repeated four or five times in duplicate and the average values were used to plot each point. An approximate 90% confidence interval for all the points was within 8% of the mean. The first order rate constant of inactivation, $k_{\text{inact}}$ was calculated by assuming the logarithmic relationship and the null hypothesis was rejected by using computer-assisted regression analysis. Protein concentration of suspensions of microsomes was determined by the Folin method (Lowry et al., 1951), using sodium deoxycholate for solubilization with bovine serum albumin as standard.

## RESULTS

The time course of ATP-dependent calcium transport by hepatic microsomal suspensions at 37 °C is shown in figure 1. Calcium transport rates were non-linear, being maximal within the first 2–3 min and slower thereafter. Non-specific ATP-independent binding of calcium by the microsomal suspensions was 3–4 nmol/mg protein and did not vary with time of incubation.

The effect of halothane on ATP-dependent transport of calcium by rat liver microsomes was examined. After pre-incubation with halothane, calcium transport was measured at 2 min after the reaction was initiated with ATP, to determine the effects of halothane on the more rapid initial rate of active calcium transport. Pre-incubation with halothane did not affect non-specific binding of calcium. The time-course of inactivation of ATP-dependent calcium transport by the microsomal suspensions during pre-incubation with varying concentrations of halothane is shown in figure 2. The results indicate that the halothane effect is

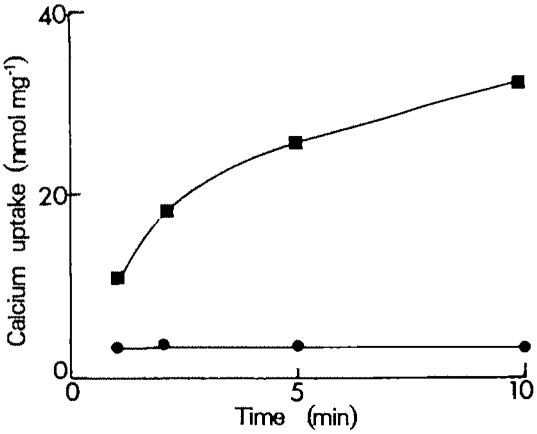

FIG. 1. ATP-dependent (■) and ATP-independent (●) calcium uptake by rat liver microsomes *in vitro*. Calcium uptake is plotted against time after the reaction was initiated.

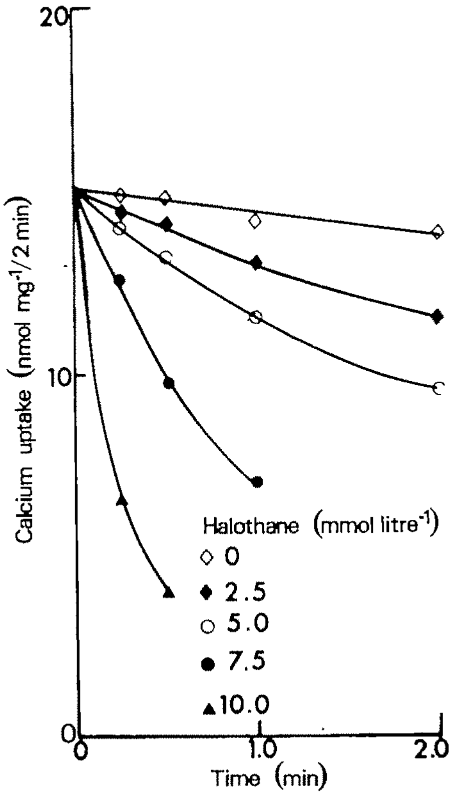

FIG. 2. The effect of time of pre-incubation with halothane on subsequent ATP-dependent calcium uptake. The $X$-axis refers to the time each aliquot was incubated with halothane. The curves represent different halothane concentrations at neutral pH (7.0).

concentration-dependent and time-dependent. The rate of inactivation of calcium transport under different conditions can be used to calculate the first order rate constant of inactivation, $k_{\text{inact}}$.

The effect of pH on the sensitivity of microsomal calcium transport to halothane inactivation was examined by repeating the experiments at pH 6.0, 6.5, and 7.0. The first order rate constant of inactivation, $k_{\text{inact}}$, of calcium transport, was calculated and plotted against concentration of halothane added to the microsomes (fig. 3). At pH 6.0 the halothane effect was enhanced and acid inactivation was additive with halothane inactivation. Analysis of variance showed the differences between pH values to be significant at the 1% level, with a mean square error term equal to 0.26. The square root of the latter term, 0.51, is the standard error averaged over all 15 points.

Removal of halothane after pre-incubation by bubbling nitrogen through the suspension for 10 min did not restore the transport activity, nor was recovery evident after exposure to atmosphere and storage of microsomes for up to 6 h at 0 °C. In control experiments, bubbling of nitrogen through the suspension did not affect calcium transport.

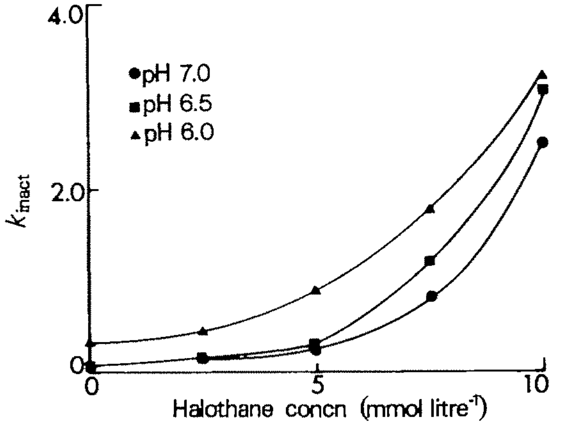

FIG. 3. The inactivation rate constant of the ATP-dependent calcium uptake by rat liver microsomes increases with increasing halothane exposure. The curves represent different pH of halothane exposure. Analysis of variance showed the difference between the pH values chosen to be significant ($P < 0.01$). The standard error averaged over all 15 points is 0.51.

## DISCUSSION

An ATP-dependent, non-linear rate of calcium transport by rat liver microsomal suspensions noted in this study confirms the findings of Bygrave (1978) of active calcium transport in liver endoplasmic reticulum. We have demonstrated that halothane inactivates calcium transport by liver microsomal suspensions at 37 °C and pH 7.0. This halothane effect is both dose-dependent and time-dependent and is irreversible under the conditions studied. Acid pH potentiates this halothane effect.

Increased cytoplasmic calcium concentrations have been recognized as one of the mechanisms whereby general anaesthetics exert their effects (Krnjevic, 1972). *In vivo* halothane inactivation of active calcium transport by endoplasmic reticulum could be one of the mechanisms that result in increased cytoplasmic calcium concentration. This could explain the finding by Biebuyck and Lund (1974) that halothane induces rapid glycogenolysis during perfused liver experiments.

Indirect support of the possible role played by increased cytoplasmic calcium in hepatotoxicity of halothane in susceptible individuals comes from studies using carbon tetrachloride ($CCl_4$) as a model for hepatotoxicity. Following *in vivo* $CCl_4$ exposure, active calcium transport by rat liver microsomes is rapidly inactivated (Moore, Davenport and Landon, 1976), and increased stainable cytoplasmic calcium was noted by Reynolds and Moslen (1974) as a separate effect to the lipoperoxidation produced.

Proposed potentiation of the halothane effect on endoplasmic reticulum calcium transport by acid environment during anaesthesia is compatible with the finding by Benumof and others (1976) of almost zero hepatic artery perfusion during halothane anaesthesia. Increased cytoplasmic calcium, which of itself would result in intracellular acidosis (Roos and Boron, 1981), could also be responsible for halothane-dependent calcium-induced loss of respiratory control (Grist and Baum, 1975). The resultant acidosis could further increase intracellular calcium concentrations (Roos and Boron, 1981), setting the stage for a vicious cycle of events. It is proposed that inactivation of calcium transport in the hypoxic centrilobular area which is relatively acid might somehow be involved in the development of centrilobular hepatic necrosis similar to the lesions seen in man and in an animal model recently described by Cousins and others (1979), following exposure in halothane hepatitis.

Several lines of evidence suggest some type of "allergic" basis for halothane hepatitis (Vergani et al., 1980). However, these events appear to have resulted from the liver injury, and not to have caused it (Dienstag, 1980). Inactivation of the calcium pump of endoplasmic reticulum or increased cytosolic calcium may contribute to such events. For example, endoplasmic reticulum calcium ATP-ase may be in equilibrium with plasma membrane calcium ATP-ase (Geisow, 1979) and halothane-induced irreversible conformational change of calcium ATP-ase (Diamond and Berman, 1980) might cause it to become antigenically reactive. Alternatively, increased cytosolic calcium concentrations may promote membrane fusion (Dreifuss, 1975) or stimulate membrane-bound calcium-activated phospholipases (Trump et al., 1980) and thus alter the antigenic properties of the plasma membrane of the hepatocyte.

Although further studies are required to compare the effect of other anaesthetic agents, we conclude that whatever the mechanism, halothane inactivation of calcium transport by hepatic endoplasmic reticulum should be considered as an explanation of some of the findings in halothane hepatitis.

## REFERENCES

Becker, G. L., Fiskum, G., and Lehninger, A. L. (1980). Regulation of free $Ca^{2+}$ by liver mitochondria and endoplasmic reticulum. *J. Biol. Chem.*, **225**, 9009.

Benumof, J. L., Bookstein, J. J., Saidman, L. J., and Harris, R. (1976). Diminished hepatic arterial flow during halothane administration. *Anesthesiology*, **45**, 545.

Berman, M. C., Harrison, G. G., Bull, A. B., and Kench, J. E. (1970). Changes underlying halothane-induced malignant hyperpyrexia in Landrace pigs. *Nature (Lond.)*, **225**, 653.

Biebuyck, J. F., and Lund, P. (1974). Effects of halothane and other anesthetic agents on the concentration of rat liver metabolites *in vivo*. *Molec. Pharmacol.*, **10**, 474.

Brown, B. R., and Sipes, I. G. (1977). Commentary: Biotransformation and hepatotoxicity of halothane. *Biochem. Pharmacol.*, **26**, 2091.

Bygrave, F. L. (1978). Properties of energy-dependent calcium transport by rat liver microsomal fractions as revealed by initial-rate measurements. *Biochem. J.*, **170**, 87.

Cousins, M. J., Sharp, J. H., Gourlay, G. K., Adams, J. F., Haynes, W. D., and Whitehead, R. (1979). Hepatotoxicity and halothane metabolism in an animal model with application for human toxicity. *Anaesth. Intens. Care*, **7**, 9.

Diamond, E. M., and Berman, M. C. (1980). The effect of halothane on the stability of $Ca^{++}$ transport activity of isolated fragmented sarcoplasmic reticulum. *Biochem. Pharmacol.*, **29**, 375.

Dienstag, J. L. (1980). Halothane hepatitis. Allergy or idiosyncrasy? *N. Engl. J. Med.*, **303**, 102.

Dreifuss, J. J. (1975). A review of neurosecretory granules: Their contents and mechanism of release. *Ann. N.Y. Acad. Sci.*, **248**, 184.

Estabrook, R. W. (1967). Mitochondrial respiratory control and the polarographic measurement of ADP: O ratios; in *Methods in Enzymology*, Vol. X. (eds S. P. Colowick and N. O. Kaplan), p. 41. New York: Academic Press.

Geisow, M. (1979). Coated vesicles. *Nature (Lond.)*, **277**, 90.

Grist, E. M., and Baum, H. (1975). Evidence for a halothane-dependent cyclic flux of calcium in rat liver mitochondria. *Eur. J. Biochem.*, **57**, 617.

Krnjevic, K. (1972). Excitable membranes and anesthetics; in *Cellular Biology and Toxicity of Anesthetics* (ed. B. R. Fink), p. 3. Baltimore: Williams & Wilkins.

Lowry, O. H., Rosebrough, N. J., Farr, A. L., and Randall, R. J. (1951). Protein measurement with the Folin phenol reagent. *J. Biol. Chem.*, **193**, 265.

Mackler, B. (1967). Microsomal DPNH-cytochrome *c* reductase; in *Methods in Enzymology*, Vol. X. (eds S. P. Colowick and N. O. Kaplan), p. 551. New York: Academic Press.

Moore, L., Chen, T., Knapp, H. R., and Landon, E. J. (1975). Energy-dependent calcium sequestration activity in rat liver microsomes. *J. Biol. Chem.*, **250**, 4562.

—— Davenport, G. R., and Landon, E. J. (1976). Calcium uptake of a rat liver microsomal subcellular fraction in response to *in vivo* administration of carbon tetrachloride. *J. Biol. Chem.*, **251**, 1197.

Reynolds, E. S., and Moslen, M. T. (1974). Chemical modulation of early carbon tetrachloride injury. *Tox. Appl. Pharmacol.*, **29**, 377.

Roos, A., and Boron, W. F. (1981). Intracellular pH. *Physiol. Rev.*, **61**, 296.

Sherlock, S. (1978). Halothane hepatitis. *Lancet*, **2**, 364.

Trump, B. F., Berezesky, I. L. K., Laiho, K. U., Osornio, A.

R., Mergner, W. J., and Smith, N. W. (1980). The role of calcium in cell injury. A review. *Scan. Electron Microsc.*, **II**, 437.

Vergani, D., Mielie-Vergani, G., Alberti, A., Neuberger, J., Eddleston, A. L. W. F., Davis, M., and Williams, R. (1980). Antibodies to the surface of halothane-altered rabbit hepatocyte in patients with severe halothane-associated hepatitis. *N. Engl. J. Med.*, **303**, 66.

## EFFETS DE L'HALOTHANE SUR LE TRANSPORT DU CALCIUM DANS DU RETICULUM ENDOPLASMIQUE ISOLE

### RESUME

Les effets de l'halothane sur le transport du calcium par des microsomes préparés à partir de foie de rat ont été étudiés. La préincubation de suspensions de microsomes en présence d'halothane inactivait de façon irréversible le transport de calcium ATP dépendant. Les effets étaient dépendants de la dose et du temps, et potentialisés en milieu acide (pH 6,0). Les effets de l'halothane, observés *in vitro*, pourraient, en augmentant les concentrations cytoplasmiques de calcium, avoir un rapport avec les effets hépatotoxiques de l'halothane.

## WIRKUNG VON HALOTHAN AUF DEN CALCIUMTRANSPORT BEI ISOLIERTE HEPATISCHE ENDOPLASMATISCHE RETICULUM

### ZUSAMMENFASSUNG

Die Wirkung von Halothan auf den Calciumtransport durch Mikrosomen, gewonnen aus der Rattenleber, wurde untersucht. Praeinkubation einer mikrosomal Suspension mit Halothan inaktivierte irreversibel den ATP-abhängigen Calciumtransport. Die Wirkung war Dosis wie Zeit abhängig und wurde verstärkt durch sauer Bedingungen (pH 6,0). Die *in vitro* beobachtete Wirkungen des Halothan kann, durch zunehmende zytosolisch Konzentration des Calcium für die leberschädlichen Effekte des Halothan von Bedeutung sein.

## EFECTOS DEL HALOTANO SOBRE EL TRANSPORTE DE CALCIO EN EL RETICULO ENDOPLASMICO Y HEPATICO AISLADO

### SUMARIO

Se analizaron los efectos del halotano sobre el transporte de calcio, efectuado por microsomas preparados a partir de higado de ratas. La incubación previa de suspensiones microsomales en presencia de halotano desactivó de forma irreversible el transporte de calcio, que está en función del ATP. Los efectos fueron dependientes de la dosis y del tiempo y se potenciaron por las condiciones ácidas (pH = 6,0). Los efectos del halotano observados *in vitro* pueden llegar a ser relevantes si se incrementan las concentraciones citosólicas.

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# SISTER CHROMATID EXCHANGES IN HUMAN LYMPHOCYTES AFTER ANAESTHESIA WITH FLUROXENE

B. HUSUM, H. C. WULF AND E. NIEBUHR

## SUMMARY

The potential mutagenicity of fluroxene was investigated by the sister chromatid exchange (SCE) test using lymphocytes in peripheral blood from patients before and after anaesthesia. Twenty-five female patients, aged 21–77 yr (median 36.5 yr) were anaesthetized for gynaecological operations with fluroxene in nitrous oxide for 60–220 min (median 110 min). The number of SCE per cell was the same before and immediately after anaesthesia. In 10 patients, SCE were examined 3 days later and no increase was observed. In nine of the other patients, SCE rates were identical before and after anaesthesia and 1 and 5 days later. It was concluded that there was no indication, from this test, of a mutagenic effect of short-term exposure to anaesthetic concentrations of fluroxene in nitrous oxide.

The possibility of a health hazard from anaesthetic agents has been discussed extensively for the last decade (reviews by Spence and Knill-Jones, 1978; Cohen, 1980; Vessey and Nunn, 1980). Experimental and epidemiological studies have indicated indirectly that working in an environment contaminated by waste anaesthetic gases may be a health hazard, but a casual relationship has never been established.

Recently, laboratory tests on mutagenicity have been used in investigations of inhalation anaesthetics (Baden et al., 1977; White et al., 1979; Baden and Simmon, 1980; Basler and Röhrborn, 1981). The sister chromatid exchange test is based on examination of the exchange of DNA material between the two chromatids in the chromosomes in mammalian cells. An increased number of such sister chromatid exchanges (SCE) reflects the influence of mutagens (Perry and Evans, 1975; Latt et al., 1979). Previous *in vitro* studies of inhalation anaesthetics by this test showed only the vinyl-containing compounds fluroxene, ethyl-vinyl ether and divinyl ether increased SCE, suggesting that the vinyl moiety might be important in this capacity (White et al., 1979).

The SCE test may also be useful for evaluation of exposure to potential mutagens *in vivo* (Latt et al., 1979; Wulf, 1980). Application of this test using lymphocytes in peripheral blood from anaesthetized humans has revealed no indication of a mutagenic effect of short-term exposure to anaesthetic concentrations of halothane or enflurane in nitrous oxide (Husum, Wilf and Niebuhr, 1981a).

In the present study, we examined SCE in lymphocytes in peripheral blood drawn from patients before and after anaesthesia with fluroxene in nitrous oxide.

## MATERIAL AND METHODS

The study was performed in 25 female patients, aged 21–77 yr (median 36.5 yr) who underwent operation for non-malignant gynaecological disease. All patients were otherwise healthy and had not received regular medication before operation. Informed consent was obtained from all patients at the preoperative visit.

A venous heparinized blood sample was taken and then anaesthesia induced with thiopentone and maintained with 3–5% fluroxene in nitrous oxide in oxygen (2:1). A second venous blood sample was taken from all patients after completion of anaesthesia. In 10 patients, a third blood sample was obtained 3 days after the operation and in nine other patients, blood samples were taken on the 1st and 5th days after operation.

The heparinized venous blood samples were labelled with code numbers so that investigators were unaware of the time of withdrawal. A 0.5-ml aliquot of blood from each sample was incubated in 9 ml of Parker 199 standard medium with 15% fetal calf serum, phytohemagglutinin (PHA) 0.2 ml and 5-bromo-2′-deoxyuridine (BrdU) $2 \times 10^{-5}$ mol litre$^{-1}$ (6 μg ml$^{-1}$). The cells were grown at 37 °C for 72 h and cell division stopped during the last 2 h

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by adding Colcemid $3 \times 10^{-7}$ mol litre$^{-1}$ to the medium. The cells were treated with hypotonic potassium chloride 75 mmol litre$^{-1}$ and fixed with glacial acetic acid in methanol (1:3). Treatment with bisbenzimide and ultraviolet light thereafter made old and newly synthesized DNA material colour differently when stained with Giemsa (Perry and Wolff, 1974; Wulf, 1980). Thirty metaphases were scored for SCE in each specimen, one SCE being counted each time two adjacent segments of a chromatid were differently coloured.

*Statistical methods* (Husum, Wulf and Niebuhr 1981b): the number of SCE in different cells of an individual person was assumed to behave as coming from a mixture of Poisson distributions. The sum of SCE in 30 cells from each patient therefore followed a Poisson distribution, and the transformation

$$y = \sqrt{\text{sum SCE}} + \sqrt{\text{sum SCE} + 1}$$

produced a normally distributed variable $y$ by which a possible effect of anaesthesia with fluroxene might be evaluated. A $t$ test was used to compare the mean values of the variable $y$ in all patients before and after anaesthesia. The mean values of $y$ at 1, 3 and 5 days after operation were compared with the corresponding values before and after anaesthesia by analysis of variance. Differences were considered to be statistically significant when $P$ was less than 0.05.

## RESULTS

Before induction of anaesthesia, the 25 patients had 9.91 ± 0.39 SCE per cell (mean ± SEM). Immediately after anaesthesia the values were 9.98 ± 0.39 SCE per cell (mean ± SEM) (table I). Ten patients had identical SCE rates before, immediately after, and 3 days after anaesthesia (table II), and nine other patients had identical SCE rates before and after anaesthesia and 1 and 5 days later (table III).

TABLE I. *Sister chromatid exchanges (SCE) in lymphocytes in 25 female patients, aged 21–77 yr (median 36.5 yr), who received fluroxene in nitrous oxide in oxygen (2:1) for 60–220 min (median 110 min)*

| | SCE per cell | | $y = \sqrt{\text{sum SCE}} + \sqrt{\text{sum SCE} + 1}$ | |
|---|---|---|---|---|
| | Mean | SEM | Mean | SEM |
| Before anaesthesia | 9.91 | 0.39 | 34.38 | 0.63 |
| After anaesthesia | 9.98 | 0.39 | 34.47 | 0.64 |

TABLE II. *Sister chromatid exchanges (SCE) in lymphocytes in 10 female patients before and after anaesthesia with fluroxene in nitrous oxide. Using analysis of variance, no statistically significant difference was observed* (F = *0.0361 with 2 and 27 degrees of freedom)*

| | SCE per cell | | $y = \sqrt{\text{sum SCE}} + \sqrt{\text{sum SCE} + 1}$ | |
|---|---|---|---|---|
| | Mean | SEM | Mean | SEM |
| Before anaesthesia | 10.36 | 0.87 | 35.01 | 1.38 |
| After anaesthesia | 10.43 | 0.81 | 35.17 | 1.30 |
| 3rd day after op. | 10.15 | 0.62 | 34.67 | 1.06 |

TABLE III. *Sister chromatid exchanges (SCE) in lymphocytes in nine female patients before and after anaesthesia with fluroxene in nitrous oxide. Using analysis of variance, no statistically significant difference was observed (F = 0.1867 with 3 and 32 degrees of freedom)*

| | SCE per cell | | $y = \sqrt{\text{sum SCE}} + \sqrt{\text{sum SCE} + 1}$ | |
|---|---|---|---|---|
| | Mean | SEM | Mean | SEM |
| Before anaesthesia | 9.84 | 0.37 | 34.33 | 0.66 |
| After anaesthesia | 9.60 | 0.47 | 33.89 | 0.82 |
| 1st day after op. | 10.09 | 0.41 | 34.76 | 0.69 |
| 5th day after op. | 10.01 | 0.61 | 34.55 | 1.03 |

## DISCUSSION

Using the Ames test (Ames, McCann and Yamasaki, 1975), Baden and colleagues (1977) found a positive mutagenicity for fluroxene but negative results for halothane and enflurane. A later study (Baden et al., 1978) confirmed that fluroxene was mutagenic to *Salmonella typhimurium* in the presence of a rat liver enzyme system, but not in the presence of human liver preparations. White and others (1979) examined SCE in Chinese hamster ovary (CHO) cells suspended in a medium containing a rat liver enzyme system. Following a 1-h exposure *in vitro* to 1 MAC of 10 inhalation anaesthetics, only the vinyl-containing compounds increased SCE. When the CHO cells were exposed to 1 MAC of each of the various agents for 24 h without liver microsomal enzymes being present, no increase in SCE was observed and therefore metabolism of the vinyl groups with formation of epoxides was thought to be the cause of the positive mutagenicity of the vinyl-containing compounds. However, in man unlike other species, fluroxene is primarily biotransformed to trifluoroacetic acid which is believed to be without serious toxic effects (Johnston et al., 1973).

In a thorough study of exposure *in vivo*, Basler and Röhrborn (1981) exposed Chinese hamsters and mice to various clinical concentrations of halothane and examined bone marrow cells for structural chromosome aberrations, micronuclei, SCE and dominant lethal mutations. They found no evidence of a mutagenic effect of halothane.

Application of the SCE test on human cells exposed *in vivo* has not revealed any change in SCE following exposure to halothane or enflurane in anaesthetic concentrations (Husum, Wulf and Niebuhr, 1981a). In the present study, we examined SCE in lymphocytes from peripheral blood in patients exposed to anaesthetic concentrations of fluroxene in nitrous oxide. Application of this method, comprising human cells exposed *in vivo*, appeared to be justified because it allowed testing of the biotransformation products of fluroxene and of the compound itself.

The study revealed no change in SCE following short-term exposure to fluroxene in anaesthetic concentrations and agrees with results of previous laboratory investigations in non-human cells exposed *in vitro* in which mutagenicity of fluroxene was demonstrated only in the presence of enzymes prepared from the livers of Aroclor 1254-pretreated rodents (Baden et al., 1978; White et al., 1979).

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## REFERENCES

Ames, B. N., McCann, J., and Yamasaki, E. (1975). Methods for detecting carcinogens and mutagens with the salmonella/mammalian-microsome mutagenicity test. *Mut. Res.*, **31**, 347.

Baden, J. M., Kelley, M., Simmon, V. F., Rice, S. A., and Mazze, R. I. (1978). Fluroxene mutagenicity. *Mutat. Res.*, **58**, 183.

—— —— Wharton, R. S., Hitt, B. A., Simmon, V. F., and Mazze, R. I. (1977). Mutagenicity of halogenated ether anesthetics. *Anesthesiology*, **46**, 346.

—— Simmon, V. F. (1980). Mutagenic effects of inhalational anaesthetics. *Mutat. Res.*, 75, 169.

Basler, A., and Röhrborn, G. (1981). Lack of mutagenic effects of halothane in mammals *in vivo*. *Anesthesiology*, 55, 143.

Cohen, E. N. (1980). *Anesthetic Exposure in the Work Place.* Littleton, Massachusetts: PSG Publishing Company.

Husum, B., Wulf, H. C., and Niebuhr, E. (1981a). Sister chromatid exchanges in lymphocytes after anaesthesia with halothane or enflurane. *Acta Anaesthesiol. Scand.*, **25**, 97.

—— —— —— (1981b). Sister chromatid exchanges in lymphocytes in women with carcinoma of the breast. *Mutat. Res.*, **85**, 357.

Johnston, R. R., Cromwell, T. H., Eger, E. I. II, Cullen, D., Stevens, W. C., and Joas, T. (1973). The toxicity of fluroxene in animals and man. *Anesthesiology*, **38**, 313.

Latt, S. A., Schreck, R. R., Loveday, K. S., and Shuler, C. F. (1979). *In vitro* and *in vivo* analysis of sister chromatid exchange. *Pharmacol. Rev.*, **30**, 501.

Perry, P., and Evans, H. J. (1975). Cytological detection of mutagen–carcinogen exposure by sister chromatid exchange. *Nature (Lond.)*, **258**, 121.

—— Wolff, S. (1974). New Giemsa method for the differential staining of sister chromatids. *Nature (Lond.)*, 257, 156.

Spence, A. A., and Knill-Jones, R. P. (1978). Is there a health hazard in anaesthetic practice? *Br. J. Anaesth.*, **50**, 713.

Vessey, M. P., and Nunn, J. F. (1980). Occupational hazards of anaesthesia. *Br. Med. J.*, **281**, 696.

White, A. E., Takehisa, S., Eger, E. I. II, Wolff, S., and Stevens, W. C. (1979). Sister chromatid exchanges induced by inhaled anesthetics. *Anesthesiology*, **50**, 426.

Wulf, H. C. (1980). Modified method for demonstrating sister chromatid exchange (SCE). *Dan. Med. Bull.*, **27**, 35.

## ECHANGES DE CHROMATIDES SOEURS DANS DES LYMPHOCYTES HUMAINS APRES UNE ANESTHESIE AU FLUROXENE

### RESUME

La mutagénicité potentielle du fluroxène a été étudiée par le test d'échange des chromatides soeurs (ECS) en utilisant des lymphocytes du sang périphérique de patients avant et après l'anesthésie. Vingt cinq femmes, âgées de 21 à 77 ans (moyenne: 36,5 ans) ont été anesthésiées pour des interventions gynécologiques au fluroxène dans le protoxyde d'azote durant 60 à 220 min (moyenne: 110 min). Le nombre d'ECS par cellule était le même avant et juste après l'anesthésie. Chez dix patientes, les ECS ont été examinés 3 jours plus tard, et aucune augmentation n'a été notée.

Chez neuf autres patientes, les fréquences d'ECS étaient les mêmes avant et après l'anesthésie et 1–5 jours plus tard. Nous en concluons que d'après ce test, il n'y a pas d'indices d'un effet mutagène d'une exposition brève à des concentrations anesthésiques de fluroxène dans le protoxyde d'azote.

## AUSTAUSCH DES SCHWESTER-CHROMATIDS IN MENSCHLICHEN LYMPHOZYTEN NACH NARKOSE MIT FLUROXEN

### ZUSAMMENFASSUNG

Die potentielle Mutagenität von Fluroxen wurde untersucht durch den Schwester-Chromatid-Austausch-Test (SCE), bei dem Lymphozyten aus dem peripheren Blut vor und nach der Narkose verwendet wurden. Fünfundzwanzig weibliche Patienten, im Alter von 21 bis 77 Jahre, (Durchschnittsalter 36,5 Jahre) wurden für gynäkologische Operationen mit Fluroxen in Lachgas für 60–220 min (im Mittel 110 min) in Narkose versetzt. Die Anzahl von SCE pro Zelle war die selbe vor und unmittelbar nach der Narkose. Bei 10 Patienten wurde SCE 3 Tage später untersucht, ohne daß ein Anstieg festzustellen war. Bei neun der anderen Patienten waren die SCE Raten vor und nach der Narkose identisch und auch 1 und 5 Tage später. Daraus konnte man schließen, daß sich hieraus kein Anzeichen für eine mutagene Wirkung einer kurzzeitigen Exposition von Fluroxen in Lachgas ergibt.

## INTERCAMBIOS CROMATIDOS GEMELOS EN LINFOCITOS HUMANOS DESPUES DE LA ANESTESIA CON FLUROXENO

### SUMARIO

Se investigó el aspecto mutagénetico potencial del fluroxeno mediante la prueba de intercambio cromátido gemelo, haciendo uso de linfocitos del riego sanguíneo periférico de los pacientes antes y después de la anestesia. Se anestesió a 25 pacientes femeninos, de edades comprendidas entre 21 y 77 años (media de 36,5 años) para someterlas a operaciones ginecológicas, utilizando para ello fluroxeno en óxido nitroso por espacio de 60 a 220 minutos (media de 110 minutos). El número de intercambios cromátidos gemelos por célula fue idéntico antes y despues de la anestesia. Se examinó el cambio cromátido gemelo en 10 pacientes al cabo de tres días sin observarse incremento alguno. En otros 9 paciente el régimen de intercambio fue idéntico antes y después de la anestesia después de transcurridos 1 y 5 días. Se concluyó que esta prueba no aportó indicación alguna de un efecto mutagenético como consecuencia de la exposición a corto plazo a concentraciones anestésicas de fluroxeno en óxido nitroso.

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# CHANGES IN CANINE INTRACRANIAL PRESSURE IN RESPONSE TO INFUSIONS OF SODIUM NITROPRUSSIDE AND TRINITROGLYCERIN

P. J. MORRIS, M. TODD AND D. PHILBIN

SUMMARY

Intracranial pressure (i.c.p.) was measured in 11 normocapnic dogs anaesthetized with thiopentone and morphine and ventilated with oxygen-enriched air. The changes in i.c.p. in response to infusions of either sodium nitroprusside (SNP) 10 $\mu$g kg$^{-1}$ min$^{-1}$ (five animals) or glyceryl trinitrate (TNG) 30 $\mu$g kg$^{-1}$ min$^{-1}$ (six animals) i.v. were recorded at a normal baseline i.c.p. and, in the same animals, once the baseline i.c.p. had been increased to 20 mm Hg and 40 mm Hg. Modest decreases (10–20%) in mean arterial pressure (m.a.p.) were noted during the infusions and the concomitant increases in i.c.p. in every animal were significant at each value of i.c.p. ($P < 0.05$). Acute pupillary dilatation was noted during SNP infusion, and further observations of pupillary changes occurring during infusion of both SNP and TNG at greater i.c.p. (60 mm Hg) emphasize the existence of trans-tentorial pressure gradients and their aggravation by the use of these agents in the presence of a very high i.c.p.

Sodium nitroprusside (SNP) has been shown to increase cerebral blood flow (c.b.f.) in animals (Ivankovitch et al., 1976) and to increase intracranial pressure (i.c.p.) in patients (Turner et al., 1977; Cottrell et al., 1978) when infused i.v. In patients in whom i.c.p. was increased because of space-occupying pathology, significantly greater increases in i.c.p. were induced. The direct-acting vasodilator hydrallazine behaves similarly (Overgaard and Skinhøj, 1975). Glyceryl trinitrate (TNG) acts on the venous rather than the arterial systemic circulation (Mason and Braunwald, 1965) and could possibly induce smaller changes in i.c.p. when used to induce systemic hypotension in neurosurgical patients (Chestnut et al., 1978). However, recent evidence from case reports (Gagnon et al., 1979) and animal studies (Rogers et al., 1979; Burt, Verniquet and Homi, 1981) confirm the ability of TNG to induce acute increases in i.c.p. This study was undertaken to compare the changes in i.c.p. in response to infusions of SNP and TNG i.v. at normal i.c.p. (< 10 mm Hg), moderately increased i.c.p. (20 mm Hg), and markedly increased i.c.p. (40 mm Hg) produced by an artificial extradural mass lesion in the dog.

## MATERIALS AND METHODS

Eleven unselected mongrel dogs weighing 14–21 kg (mean 17.3 kg) were studied. Anaesthesia was induced with a loading dose of thiopentone 25 mg kg$^{-1}$ i.v. administered over 2–3 min, and maintained by a continuous infusion of thiopentone 5 mg kg$^{-1}$ h$^{-1}$ supplemented by morphine sulphate 1.5 mg kg$^{-1}$ i.v. in divided doses. Suxamethonium 1 mg kg$^{-1}$ was administered initially and the lungs ventilated mechanically (Harvard Instruments small animal ventilator) via a cuffed endotracheal tube with oxygen-enriched room air at a tidal volume of 12–15 ml kg$^{-1}$ and a rate sufficient to maintain normocapnia (mean arterial carbon dioxide tension ($Pa_{CO_2}$) 5.28 kPa ± SEM 0.32). Arterial oxygen tension was maintained between 20 and 30 kPa. Pancuronium bromide was given intermittently in increments of 0.2–0.4 mg i.v. to abolish spontaneous ventilation. An infusion of lactated Ringer's solution 4 ml kg$^{-1}$ h$^{-1}$ was given throughout the experiment. Oesophageal temperature, monitored with a thermistor probe (Yellow Springs Instruments), was maintained between 37 and 38.5 °C (37.75 °C ± 0.09, mean ± SEM) using heating lamps.

Arterial pressure was measured in the abdominal aorta via a catheter inserted in the femoral artery and connected to a Statham transducer recording on a Grass polygraph. The zero reference was taken as

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the level of the heart. Mean pressures were obtained by electronic damping and the end-expiratory values reported. Arterial blood was intermittently sampled from the contralateral femoral artery for blood-gas analysis.

Through a midline scalp incision the temporal muscles were reflected on both sides of the skull, and bilateral parietal burr holes (approximately 8 mm in diameter) were made to expose the underlying dura. On one side a fine, blunt-tipped, saline-filled polyethylene tube with multiple side holes (Argyle 5F-gauge paediatric feeding tube) was passed through a small dural incision into the subarachnoid space overlying the parietal cortex. A c.s.f.-tight seal was achieved by the catheter itself, and the burr hole was closed with quick set epoxy cement reinforced with heavy gauge aluminium foil. Through the contralateral burr hole a balloon-tipped Foley catheter was inserted to the extradural space. As the volume of the uninflated balloon catheter tip was approximately 0.4 ml it was inserted following completion of the measurements of i.c.p. which related to the effects of the drugs on normal i.c.p.

Measurements of i.c.p. were obtained from the subarachnoid space via the polyethylene tube, using a Statham pressure transducer with the zero reference point at the parietal burr hole. All measurements were made in the supine position with the animal's head adjusted to place the i.c.p. zero reference point level with the mid thorax.

Two groups of identically prepared animals were studied. Five animals received infusions of SNP i.v., and six animals received TNG i.v. The changes in i.c.p. in response to the drugs were studied before the insertion of the extradural balloon, that is at a normal i.c.p. and, following insertion of the balloon, under conditions of increased i.c.p. The drugs were infused to the inferior vena cava via a catheter in a femoral vein, and using an infusion pump (Harvard Instruments). SNP was infused initially at a rate of 0.5 $\mu$g kg$^{-1}$ min$^{-1}$, and the rate of infusion was incrementally increased every 2 min, until a rate of 10 $\mu$g kg$^{-1}$ min$^{-1}$ was attained, the incremental rates being 0.5, 1.0, 2.0, and 5.0 $\mu$g kg$^{-1}$ min$^{-1}$. The 10 $\mu$g kg$^{-1}$ min$^{-1}$ infusion was maintained for 2 min and discontinued abruptly. The changes induced in m.a.p. and i.c.p. were recorded. Following recovery of i.c.p. and m.a.p. (a minimum period of 30 min was allowed) the extradural balloon was inserted and slowly inflated with water at a rate of 50 $\mu$litre min$^{-1}$ until a stable i.c.p. of 20 mm Hg was attained. SNP was infused as previously and following a further period of recovery i.c.p. was increased further to achieve a stable value of 40 mm Hg by further inflation of the balloon. The infusion of SNP was repeated. An identical procedure was followed in the six animals receiving the infusion of TNG, although higher doses of TNG were used to produce similar changes in m.a.p. The rate of infusion of TNG was commenced at 1.5 $\mu$g kg$^{-1}$ min$^{-1}$ and increments of 3.0, 6.0 and 15 $\mu$g kg$^{-1}$ min$^{-1}$ were given to a maximum dose of 30 $\mu$g kg$^{-1}$ min$^{-1}$. The changes in i.c.p. were assessed for significance using Student's *t* test for paired data.

Following the observation in one animal that an increase in i.c.p. of more than 70 mm Hg from a baseline value of 40 mm Hg was associated with fixed pupillary dilatation during SNP infusion, it was decided to increase further the i.c.p. in two of the SNP animals and four of the TNG animals to 60 mm Hg by inflation of the balloon, and then observe any further response of i.c.p. and any changes in the pupils to a 2-min infusion of the respective drugs at their maximum infusion rates. No statistical evaluation of these observations was attempted.

## RESULTS

Both groups of animals demonstrated similar modest decreases in m.a.p. during the infusion of the drugs (table I). Each administration of either SNP or TNG produced an increase in i.c.p. in every animal at each value of i.c.p. (fig. 1). As one would expect, the absolute values of the increases in i.c.p. became greater as the baseline i.c.p. was increased, reflecting the decreased intracranial compliance as the extradural mass was expanded (Fitch and McDowall, 1971). Of the six animals receiving TNG measurements from one were excluded from figure 1 at normal i.c.p. as the dose rate used was only 15 $\mu$g kg$^{-1}$ min$^{-1}$, and a further animal was excluded at a baseline i.c.p. of 20 mm Hg as spontaneous respiration occurred during the infusion. However, both animals did show appropriate increases in i.c.p.

One animal, indicated by the arrow in figure 1, deserves special comment as the i.c.p. in this animal increased from 40 mm Hg to 76 mm Hg during the infusion of SNP 10 $\mu$g kg$^{-1}$, but abruptly decreased to 56 mm Hg before cessation of the infusion. Associated with this was a sudden, full dilatation of both pupils and the animal's i.c.p. was noted to be pressure-passive following this event. It was concluded that acute herniation of the supratentorial contents had occurred across the tentorium. Two

TABLE I. *Changes in mean arterial pressure (MAP), $P_{aCO_2}$ and $P_{aO_2}$ with drug infusion (mean ± SEM).* n = *5 for all except*†, *when* n = *6.* **Significant decrease in MAP during infusion: 0.05 > P > 0.01*

| | Baseline ICP | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 10 mm Hg | | | 20 mm Hg | | | 40 mm Hg | | |
| Drug infused | MAP (mm Hg) | $P_{aCO_2}$ (kPa) | $P_{aO_2}$ (kPa) | MAP (mm Hg) | $P_{aCO_2}$ (kPa) | $P_{aO_2}$ (kPa) | MAP (mm Hg) | $P_{aCO_2}$ (kPa) | $P_{aO_2}$ (kPa) |
| SNP | | | | | | | | | |
| Control | 121.0<br>±6.9 | 5.27<br>±0.09 | 23.3<br>±1.1 | 130.0<br>±6.6 | 5.22<br>±0.17 | 22.2<br>±0.9 | 125.0<br>±2.9 | 5.22<br>±0.15 | 23.0<br>±0.5 |
| Infusion | 101.0<br>±7.1 | 5.38<br>±0.11 | 21.5<br>±1.3 | 102.0<br>±5.4 | 5.25<br>±0.18 | 20.6<br>±2.0 | 99.0*<br>±4.6 | 5.28<br>±0.20 | 21.0<br>±2.0 |
| TNG | | | | | | | | | |
| Control | 115.0<br>±6.7 | 5.32<br>±0.13 | 24.4<br>±1.5 | 123.0<br>±4.9 | 5.0<br>±0.13 | 24.5<br>±1.6 | 128.0†<br>±4.1 | 5.22†<br>±0.11 | 23.6†<br>±0.9 |
| Infusion | 102.0<br>±4.7 | 5.38<br>±0.13 | 23.9<br>±1.1 | 105.0<br>±5.6 | 5.14<br>±0.15 | 22.7<br>±1.5 | 111.0†<br>±6.8 | 5.13†<br>±0.10 | 22.2†<br>±0.6 |

TABLE II. *Changes in ICP (mm Hg) with drug infusion (mean ± SEM). All changes in ICP were significant:* *P < *0.05;* **P < *0.01;* ***P < *0.001*

| | Baseline ICP | | | | | |
|---|---|---|---|---|---|---|
| | 10 mm Hg | | 20 mm Hg | | 40 mm Hg | |
| Drug infused | Control | Infusion | Control | Infusion | Control | Infusion |
| SNP | 8.7<br>±0.6 | 14.5*<br>±1.7 | 20.6<br>±0.5 | 34.0**<br>±1.8 | 40.0<br>±0.5 | 59.0***<br>±1.25 |
| TNG | 8.4<br>±0.7 | 16.3*<br>±2.0 | 20.3<br>±0.6 | 33.9*<br>±2.1 | 40.5<br>±0.3 | 58.0*<br>±4.3 |

further animals also developed acute, but less severe pupillary changes during infusion at baseline i.c.p. of 40 mm Hg. One received SNP and developed a peak i.c.p. of 62 mm Hg, and the other received TNG and developed a peak i.c.p. of 65 mm Hg. The pupillary changes resolved on stopping the administration of the drug and with the return of the i.c.p. towards baseline.

Of the six animals subjected to an i.c.p. of 60 mm Hg, one animal of the four TNG animals developed acute pupillary changes during the inflation of the balloon. In the remaining three animals i.c.p. increased to more than 80 mm Hg during the infusion of TNG, and these increases were associated with bilateral pupillary dilatation in all three animals. The two SNP animals developed pupillary changes during drug infusion at this value of i.c.p., one animal developing fixed dilated pupils, while the other demonstrated transient unilateral right pupillary dilatation which resolved on terminating the infusion.

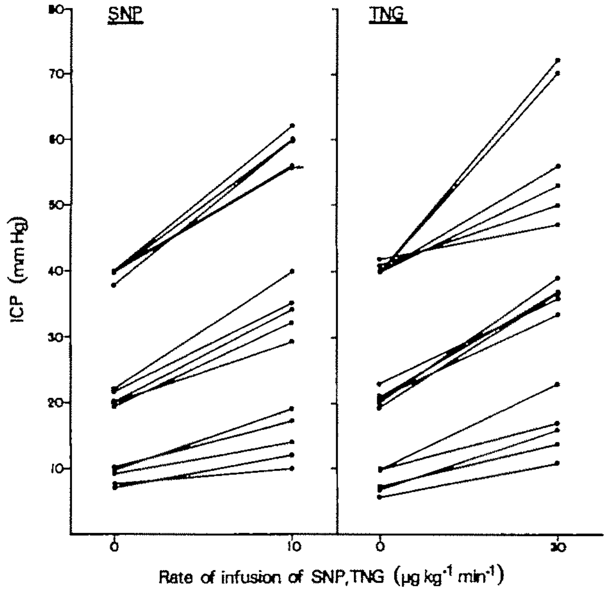

FIG. 1. Changes in intracranial pressure in response to infusion of sodium nitroprusside 10 $\mu$g kg$^{-1}$ min$^{-1}$ and glyceryl trinitrate 30 $\mu$g kg$^{-1}$ min$^{-1}$. For explanation of arrow, see text—Results.

## DISCUSSION

The results of these experiments are in broad agreement with the findings of other workers, namely that TNG i.v. will induce consistent increases in i.c.p. in animals (Rogers et al., 1979; Writer et al., 1980). However, our findings are in conflict with those of Burt, Verniquet and Homi (1981) who, using greyhounds anaesthetized in a manner similar to that used in this investigation, demonstrated very modest increases in i.c.p. (about 3 mm Hg) from a baseline i.c.p. of 12 mm Hg, and decreases in i.c.p. were noted with bolus doses of TNG in animals with extradural mass lesions when m.a.p. was decreased acutely by more than 25% from control. The slight hypocapnia described in their paper is unlikely to be the cause of this difference. No mention is made of the position of the head by Burt, Verniquet and Homi, and it is possible that the supine position contributed to the increases in i.c.p. seen in our animals. However, the work of Rogers and colleagues was performed with the animals in the head-up position and this, together with the increase in i.c.p. observed even at high baseline i.c.p., would seem to be presumptive evidence against the venodilator action of TNG being of importance in the cerebral circulation. Recent work by Fitch and his co-workers (Fitch, personal communication) has demonstrated the ability of TNG to increase c.b.f. significantly in primates. The observations of Burt and colleagues are in agreement in some respects with those of Turner and colleagues (1977) who observed decreases in i.c.p. in patients with mass lesions when SNP was used to decrease m.a.p. by more than 30% of control.

The explanation for these conflicting observations probably lies in the dosage and mode of administration of the drugs used. The decrease in m.a.p. with bolus administration of the drug may be sufficiently rapid to prevent the increase in cerebral blood flow/volume required to produce an increase in i.c.p. A major factor involved in the increases in i.c.p. recorded by us must be the modest decreases in m.a.p. seen in all animals, amounting to less than 20% of control. The combination of drug-induced cerebral vasodilatation in conjunction with a maintained perfusion pressure would induce an increase in c.b.f. and i.c.p., and our data represent the worst situation. That such changes occur clinically has been shown by the case report of Gagnon and colleagues (1979): the change in i.c.p. from 25 mm Hg to 48 mm Hg induced by intranasal TNG in a patient with a space-occupying lesion is in close agreement with our observations. It must also be noted that oral TNG frequently causes headache in patients.

The experiments performed at baseline i.c.p. of 60 mm Hg are of little relevance to the clinical situation, but as stated by Fitch and McDowall (1971) in relation to halothane, "pupillary dilation is frequently the sign which indicates the presence of an acute expanding intracranial mass; the clinical conclusion to be drawn is that the injudicious use of halothane may, on occasions, lead to brain shift and tentorial impaction in patients with undiagnosed space occupying lesions." The pupillary dilatation seen with the infusion of both SNP and TNG at these values parallels the observations with halothane, and the contraindication to the use of these agents and other direct-acting vasodilators in patients with increased i.c.p. is emphasized.

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## REFERENCES

Burt, D. E. R., Verniquet, A. J. W., and Homi, J. (1981). Effects of nitroglycerin-induced hypotension on intracranial pressure in dogs. *Br. J. Anaesth.*, 53, 186.

Chestnut, J. S., Albin, M. S., Conzales-Abola, E., Newfield, P., and Maroon, J. C. (1978). Clinical evaluation of intravenous nitroglycerin for neurosurgery. *J. Neurosurg.*, 48, 704.

Cottrell, J. E., Patel, K., Turndorf, H., and Ransohoff, J. (1978). Intracranial pressure changes induced by sodium nitroprusside in patients with intracranial mass lesions. *J. Neurosurg.*, 48, 329.

Fitch, W., and McDowall, D. G. (1971). Effect of halothane on intracranial pressure gradients in the presence of intracranial space occupying lesions. *Br. J. Anaesth.*, 43, 904.

Gagnon, R. L., Marsh, M. L., Smith, R. W., and Shapiro, H. M. (1979). Intracranial hypertension caused by nitroglycerine. *Anesthesiology*, 51, 86.

Ivankovitch, A. D., Miletich, D. J., Albrecht, R. F., and Zaned, B. (1976). Sodium nitroprusside and cerebral blood flow in the anesthetized and unanesthetized goat. *Anesthesiology*, 44, 21.

Mason, D. T., and Braunwald, E. (1965). The effects of nitroglycerin and amyl nitrate on arteriolar and venous tone in the human forearm. *Circulation*, 32, 755.

Overgaard, J., and Skinhøj, E. (1975). A paradoxical cerebral haemodynamic effect of hydrallazine. *Stroke*, 6, 402.

Rogers, M. L., Hamburger, C., Owen, K., and Epstein, M. H. (1979). Intracranial pressure in the cat during nitroglycerin-induced hypotension. *Anesthesiology*, 51, 227.

Turner, J. M., Powell, D., Gibson, R. M., and McDowall, D. G. (1977). Intracranial pressure changes in neurosurgical patients during hypotension induced with sodium nitroprusside or trimetaphan. *Br. J. Anaesth.*, 49, 419.

Writer, W. D. R., James, F. M., Stulken, E. H., and Koontz, F. A. (1980). Intracranial effects of nitroglycerin: an obstetrical hazard. *Anesthesiology*, 53, S309.

## MODIFICATIONS DE LA PRESSION INTRACRANIENNE CHEZ LE CHIEN EN REPONSE A DES PERFUSIONS DE NITROPRUSSIATE DE SODIUM ET DE TRINITROGLYCERINE

### RESUME

La pression intracranienne (PIC) a été mesurée chez 11 chiens normocapniques anesthésiés au thiopental et à la nalorphine et ventilés à l'air enrichi en oxygène. Les modifications de la PIC en réponse à des perfusions i.v. soit de nitroprussiate de sodium (NPS) 10 $\mu$g kg$^{-1}$ min$^{-1}$ (cinq animaux) soit de trinitroglycérine (TNG) 30 $\mu$g kg$^{-1}$ min$^{-1}$ (six animaux) ont été enregistrées en partant d'une PIC de base normale et, chez les mêmes animaux, après avoir élevé la PIC de base à 20 et à 40 mm Hg. Des diminutions modérées (10–20%) de la pression artérielle moyenne ont été notées pendant les perfusions et les augmentations concomittantes de la PIC chez chaque animal étaient significatives quelque soit la PIC initiale ($P < 0{,}05$). Une mydriase aiguë a été notée pendant la perfusion de NPS et l'observation ultérieure d'autres modifications pupillaires au cours de perfusions de NPS et de TNG pour des PIC plus élevées (60 mm Hg) souligne l'existence de gradients de pression à travers la tente et leur aggravation par l'utilisation de ces agents en présence d'un PIC très élevée.

## VERÄNDERUNGEN DES INTRAKRANIELLEN DRUCKES VON HUNDEN NACH INFUSION VON NATRIUMNITROPRUSSID UND TRINITROGLYZERIN

### ZUSAMMENFASSUNG

Der intrakranielle Druck (ICP) wurde bei elf normokapnischen Hunden, die mit Thiopental und Morphium anästhesiert und mit Sauerstoff angereicherter Luft beatmet wurden, gemessen. Die Veränderungen des ICP nach i.v. Infusion von entweder Natriumnitroprussid (SHP) 10 $\mu$g kg$^{-1}$ min$^{-1}$ (fünf Tiere) oder von Glyzeryltrinitrat (TNG) 30 $\mu$g kg$^{-1}$ (sechs Tiere) wurden auf einer normalen ICP Grunlinie aufgezeichnet und bei den selben Tieren, wenn die Grundlinie auf 20 mm Hg und auf 40 mm Hg angestiegen war, noch einmal aufgetragen. Mäßige Abfälle des mittleren arteriellen Druckes (10–20%) waren während der Infusionen zu beobachten und die damit einhergehende Erhöhung des ICP war signifikant ($P < 0{,}05$). Während der SNP Infusion fiel eine akute Pupillenerweiterung auf. Die weitere Beobachtung der Pupillenweite während der SNP- und TNG- Infusionen betont das Vorhandensein von trans-tentoriellen Druckgradienten und deren Verstärkung durch Verwendung dieser Pharmaka in Anwesenheit eines sehr hohen ICP.

## CAMBIOS EN LA PRESION INTRACRANEANA DE CANINOS COMO RESPUESTA A INFUSIONES DE NITROPRUSIATO DE SODIO Y DE TRINITROGLICERINA

### SUMARIO

Se midió la presión intracraneana (p.i.c.) en 11 perros normocápnicos anestesiados con tiopentona y morfina, y ventilados con aire enriquecido con oxígeno. Los cambios en la presión intracraneana, como respuesta a las infusiones de 10 $\mu$g kg$^{-1}$ min$^{-1}$ (cinco animales) de nitroprusiato de sodio (NPS) o de 30 $\mu$g kg$^{-1}$ min$^{-1}$ (seis animales) de trinitrato de glicerilo (TNG), administrados intravenosamente, se registraron en la línea de base normal de la presión intracraneana y, en los mismos animales, después de haber incrementado dicha línea de base a 20 mm Hg y a 40 mm Hg. Se apreciaron ligeras disminuciones (del 10% al 20%) en la presión arterial media (p.a.m.) durante las infusiones y los incrementos concomitantes en la p.a.m. de cada animal fueron significativos en cada una de las p.a.m. ($P < 0{,}05$). Se apreció una aguda dilatación pupilar durante la infusión del NPS, y las otras observaciones de cambios pupilares que tuvieron lugar durante la infusión de NPS y de TNG a p.i.c. superiores (60 mm Hg) ponen de relieve la existencia de gradientes de presión trans-tentoriales así como su agravación por el uso de estos agentes en presencia de una p.i.c. muy elevada.

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# STEREOPHOTOGRAMMETRIC EVALUATION OF TRACHEAL VOLUMES IN THE RABBIT

S. LINDAHL, E. RANKLEV, G. SELVIK, AND L. EKELUND

## SUMMARY

The feasibility and precision of x-ray stereophotogrammetry for studies of airway volumes were investigated after insertion of tantalum balls into the rabbit tracheal wall. Tracheal volume changes at different ventilator settings during anaesthesia and artificial ventilation were evaluated. The precision of the method was high and even small volume changes caused by different ventilatory frequencies at unchanged alveolar ventilation were detected. Tracheal volume was maximal at positive end-expiratory pressures of more than 1.0 kPa and at end-inspiratory tracheal pressures greater than 3.0 kPa. The absence of increased tracheal volumes at higher pressures might be caused by elastic properties of the airways. X-ray stereophotogrammetry allows precise measurements of tracheal volumes and the method might be useful in clinical situations in which tracheal volume changes are of interest.

Tracheal and bronchial movements are associated with the phase of the respiratory cycle (Macklin, 1932; Fraser, 1961). Previous reports of the interaction between airway diameters and distending pressures have not been able to show conclusively where and to what extent different airways are influenced (Bickerman et al., 1952; Gayrard, Leonardelli and Noirclere, 1969). The lack of agreement between different studies might be caused by difficulties in the quantitative measurement of changes in the dimensions of elastic circular organs.

By the use of x-ray stereophotogrammetry as described by Selvik (1974), measurements of bone growth can be made with a high level of precision (Aronson, Hansson and Selvik, 1978). This method has also been shown to be valid for evaluation of liver volume in different clinical situations and for evaluation of tumour size (Claesson et al., 1978; Tropé et al., 1978). The purpose of this study was to evaluate the feasibility and precision of this method in determination of tracheal volume changes during artificial ventilation.

## MATERIAL AND METHODS

The technique of x-ray stereophotogrammetry developed by Selvik (1974) was used in this study with tantalum balls 0.5 mm diameter as markers. After dissection of the rabbit trachea, just above the manubrium, eight balls were placed in the cartilage of the tracheal wall, 1 week before the investigation. A plastic cannula 1 mm diameter was used to facilitate insertion of the balls. The markers were arranged within the extrathoracic tracheal wall to describe a well-defined polyhedron, representative of the geometry of the ventral part of the trachea.

A rabbit (weight 2.5 kg) was anaesthetized for the investigation with pentobarbitone 20 mg kg$^{-1}$ and nitrous oxide in oxygen ($F\text{I}_{\text{O}_2}$ 0.3). Tracheotomy was performed at the cricoid level well above the tantalum balls and a cuffed plastic tracheal tube inserted. Alcuronium 1 mg was given for muscle relaxation when needed. A TVM ventilator was used (Lindahl and Okmian, 1979) to ventilate the lungs. Arterial blood was sampled from a catheter placed in the femoral artery. External abdominal pressure was applied with a calibrated pressure cuff placed just below the costal margin.

To follow changes in shape of the polyhedron, the animal was placed in a specially constructed calibration box (fig. 1). The markers' positions in a three-dimensional coordinate system were determined by simultaneously exposing the markers from two x-ray tubes on one film. After film measurements and computer calculations of marker co-ordinates, the volume of a polyhedron defined by the markers was obtained and its projections plotted on the co-ordinate planes. Using an optimization procedure in the computer program, the stereo model of the markers was reoriented to the best fit by the least-squares method (Selvik, 1974) with the initial examination at atmospheric pressure (fig. 2).

## PROCEDURE

The tracheal volume (the volume in mm$^3$ of the

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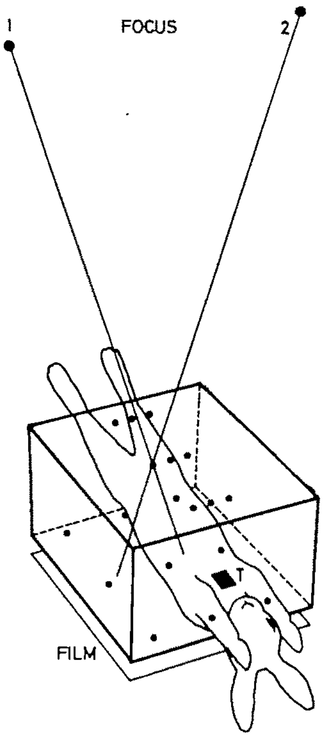

FIG. 1. X-ray stereophotogrammetric examination of the rabbit in the calibration box. Reference markers in two planes of the box are indicated. T = region of trachea where the tantalum balls are implanted in the ventral two-thirds of the cartilage. The stereophotogrammetrically calculated positions of the eight balls, projected on the frontal (film) plane and on the transverse plane, are shown in figure 2.

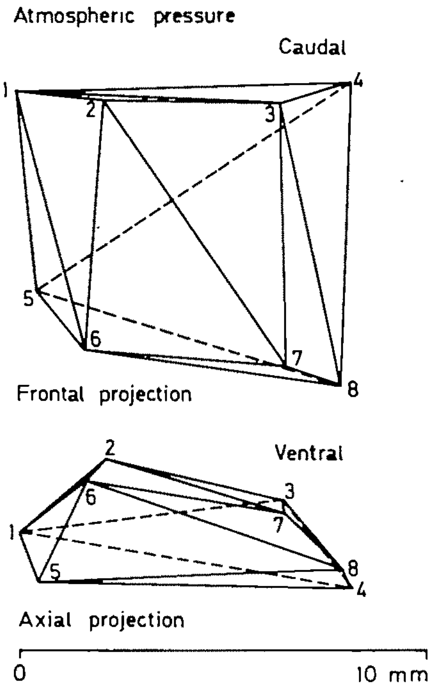

FIG. 2. Tracheal marker configuration at atmospheric pressure. Balls are numbered 1–8. The lateral projection is not shown. The axial projection is seen from the head. Connecting lines between the edges of the polyhedron that are not seen in the two views are shown by broken lines. The volume was 90.0 mm$^3$.

polyhedron) at atmospheric pressure was used as a reference standard. The rapidly decelerated inspiratory flow achieved with the TVM ventilator resulted in an end-inspiratory plateau pressure ($P$I′ fig. 3) being achieved within 0.3–0.4 s. With an inspiration time of 1.0 s, the plateau phase had a duration of 0.6–0.7 s. Thus, the plateau was well defined and was indicated by a lamp on the ventilator, which facilitated x-ray exposures (exposure time 0.04 s) simultaneous with the static end-inspiratory plateau phase. The different ventilator settings used for the study of tracheal volumes were:

I: Ventilatory frequencies ($f$) and inspiration times ($t$): $f = 10$, 20 and 30 cycles min$^{-1}$ and $t = 1.2$, 1.0 and 1.0 s, respectively, at an unchanged alveolar ventilation ($Pa_{CO_2}$ 3.4–3.6 kPa).

II: Different positive end-expiratory pressures (PEEP) at $f = 20$ cycles min$^{-1}$ and $t = 1.0$ s: 0.5, 1.0 and 1.5 kPa.

III: Different end-inspiratory tracheal pressures at $f = 20$ cycles min$^{-1}$ and $t = 1.0$ s: 1.0, 2.0, 3.0, 4.0 and 5.0 kPa.

IV: Ventilation at $f = 20$ cycles min$^{-1}$ and $t = 1.0$ s with and without external abdominal pressure of 4.0 kPa.

## RESULTS

### *Precision test*

By evaluating nine of the films and comparing the differences in marker distances and volumes between the two evaluations of each film, the standard deviations for distance between markers and polyhedron volume was found to be 27 µm and 0.73 mm$^3$, respectively.

### *Volume variations*

The tracheal volume at atmospheric pressure was 90.0 mm$^3$.

*Ventilatory frequencies.* At an unchanged alveolar ventilation, tracheal volume increased at greater ventilatory frequencies, in spite of larger $P$I′ at lower frequencies (table I).

TABLE I. *Tracheal volumes at different ventilator settings (I, II, III, IV–see text). * Use of external abdominal pressure*

| | I | | | II | | | III | | | | | IV | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $f$ (cycles min$^{-1}$) | 10 | 20 | 30 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 * |
| % Inspir | 20 | 33 | 50 | 33 | 33 | 33 | 33 | 33 | 33 | 33 | 33 | 33 | 33 * |
| $P_{I}'$ (kPa) | 1.7 | 1.0 | 0.8 | 2.4 | 2.8 | 3.2 | 1.0 | 2.0 | 3.0 | 4.0 | 5.0 | 1.0 | 4.4* |
| PEEP (kPa) | — | — | — | 0.5 | 1.0 | 1.5 | — | — | — | — | — | — | — |
| $P_{aCO_2}$ (kPa) | 3.6 | 3.4 | 3.4 | — | — | — | — | — | — | — | — | 3.4 | 3.5* |
| Tracheal volume (mm$^3$) | 92.7 | 93.9 | 96.8 | 96.6 | 104.6 | 101.2 | 89.5 | 97.7 | 104.7 | 103.7 | 104.1 | 93.9 | 111.9* |

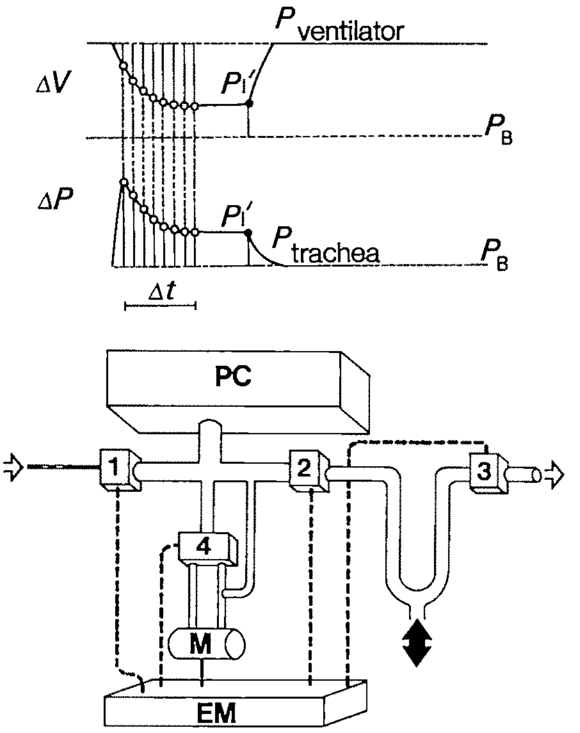

FIG. 3. The ventilator: 1 = filling valve; 2 = inspiratory valve; 3 = expiratory valve; 4 = differential pressure manometer; PC = pressure chamber; M = manometer; EM = electronic module for synchronization of the valve function. Open arrows denote gas inlet and outlet. Filled arrow denotes the tracheal connection. Above: Schematic pressure curves from PC and from the tracheal tube connection. Volume changes in PC ($\Delta V$) and corresponding tracheal pressure changes ($\Delta P$) during insufflation are indicated. $P_B$ = atmospheric pressure.

*PEEP.* At the same ventilatory frequency ($f$ = 20), the tracheal volume at $P_I'$ 2.0 kPa without PEEP was 97.7 mm$^3$. With the addition of 0.5 kPa PEEP, the volume was unchanged (96.6 mm$^3$). At a PEEP of 1.0 kPa the volume of the polyhedron increased to 104.6 mm$^3$, an increase of 7.1% compared with no PEEP. At a PEEP of 1.5 kPa, no further increase in tracheal volume was found (table I).

*$P_I'$.* At $P_I'$ 1.0 kPa, tracheal volume was virtually unchanged compared with atmospheric conditions. $P_I'$ 2.0 kPa increased tracheal volume by 9.2% from 89.5 to 97.7 mm$^3$. At $P_I'$ 3.0 kPa the volume was 104.7 mm$^3$. $P_I'$ of 4.0 and 5.0 kPa did not further increase the polyhedron volume (table I, fig. 4).

*Abdominal pressure.* After application of an external pressure of 4.0 kPa at an unchanged alveolar ventilation ($P_{aCO_2}$ 3.4 kPa), $P_I'$ increased from 1.0 to 4.4 kPa. Under these circumstances, tracheal volume increased by 19.2% from 93.9 to 111.9 mm$^3$ (table I, fig. 5).

## DISCUSSION

The precision of the measurements presented refers to the reliability of the photogrammetric process. Thus, the accuracy of reported distance and volume variations refer to the marker configuration and only indicate tracheal changes if the markers are stable in the cartilage. In rigid tissue such as bone, stability can be checked by calculating distance variations between markers in each bone segment (Rune et al., 1979). In deformable tissue such as cartilage, control of stability was obtained by inserting the markers 1 week before the investigation in order to permit healing of the insertion channel. With this arrangement, the markers were considered stable at the time of the study and their movements represented changes in the ventral two-thirds of the trachea.

During positive pressure ventilation, Bickerman and others (1952) demonstrated an increase of the cross-sectional diameters of the entire bronchial tree. The increase was more pronounced in small bronchi than in the trachea. However, Gayrard, Leonardelli and Noirclere (1969) found that the tracheal diameter decreased with positive pressure inflation in anaesthetized dogs. The contradiction of these earlier results might be explained by the methods used. In both the Bickerman and the Gayrard studies, three-dimensional evaluations of

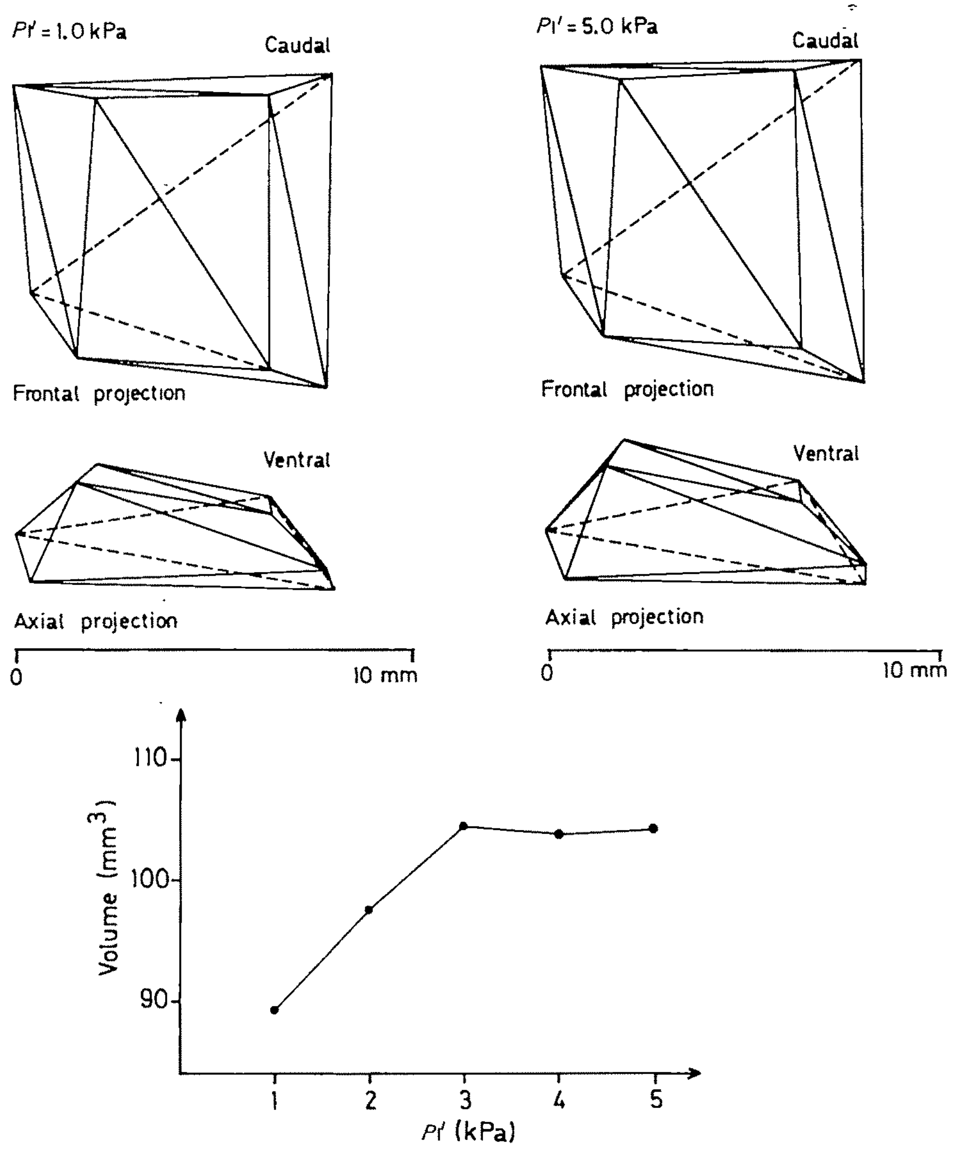

FIG. 4. Top: Tracheal marker configuration at a Pl' of 1.0 and 5.0 kPa. The volumes are 89.5 and 104.7 mm$^3$, respectively. Bottom: Variation of tracheal volume with Pl'.

the airways were not performed. The abdominal traction during inspiration might have caused changes in shape of the airways which were not observed two-dimensionally thus making a three-dimensional estimation of airway changes during positive pressure ventilation a more appropriate method to use.

In a study by Hughes, Hoppin and Mead (1972), a three-dimensional method was used to measure airway length and diameter in excised lung. They found that bronchial changes were larger if pulmonary tissue was not dissected free from the airway, compared with measurements in isolated bronchi (Martin and Proctor, 1958). However, the behaviour of airway mechanics is complex and depends not only on elastic properties of the airways, but also on lung perfusion and, as shown by Hahn, Graf and Nadel (1976), on vagal tone. Therefore, conclusions from *in vitro* studies are probably not valid *in vivo*.

Apart from being a three-dimensional method, x-ray stereophotogrammetry also allows quantita-

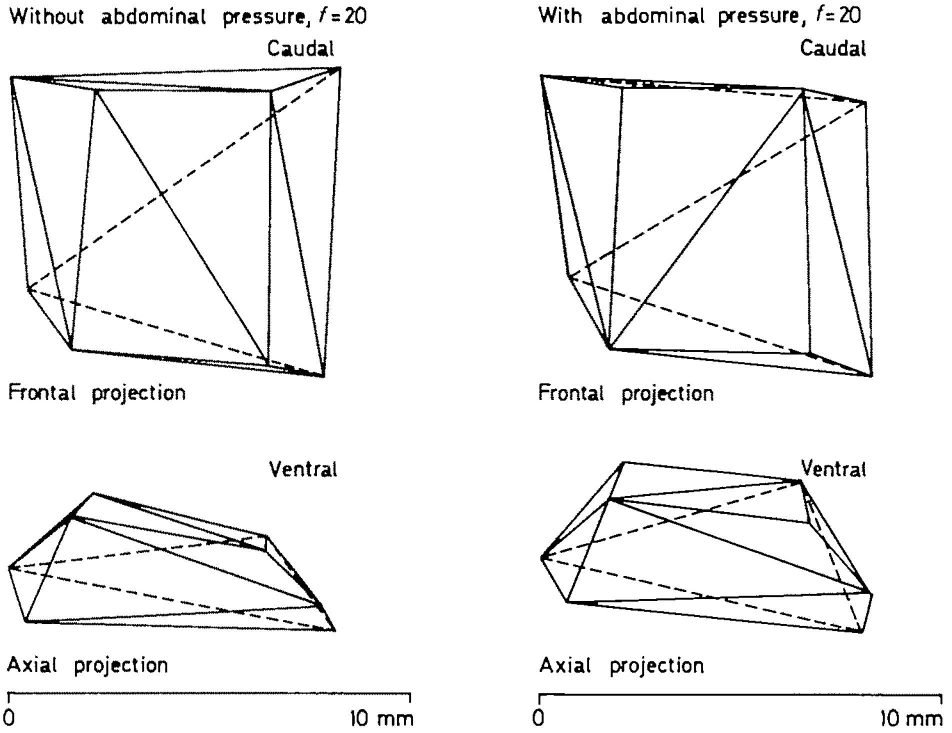

FIG. 5. Tracheal marker configuration during inspiration at $f = 20$ cycles $\min^{-1}$ with and without abdominal pressure. The volumes were 93.9 and 111.9 $\text{mm}^3$, respectively.

tive volume measurements *in vivo*. It was found that extrathoracic tracheal volumes were larger at higher ventilatory frequencies in spite of lower $P_T'$ (table I). This might result from incomplete exhalation at higher frequencies with shorter expiration times which has been shown in the normal piglet lung (Arborelius and Lindahl, 1980). This explanation is also supported by the mean airway pressure which, with a squarewave tracheal pressure profile, was 0.28 kPa at $f = 10$ and 0.40 kPa at $f = 30$ cycle $\min^{-1}$. However, measured tracheal volume variations were small (table I).

During artificial ventilation with PEEP, FRC increases and tracheal volumes were found to be greater. However, tracheal volume did not increase linearly with PEEP, and increasing PEEP from 1.0 to 1.5 kPa did not result in any further increase of tracheal volume. Similarly, when the effects of successive increases of $P_T'$ were studied, the maximal tracheal volume was measured at $P_T'$ approximately 3.0 kPa (fig. 4). These results could be explained by an elastic limitation to the distending forces, since the $P_T'$ found was compatible with the tracheal pressure (30 cm $H_2O$) known to cause interstitial emphysema in anaesthetized dogs (Ovenfors, 1964).

When abdominal excursions were limited by external abdominal pressure, the tracheal volume increased by almost 20% during periods of unchanged alveolar ventilation. This increase in tracheal volume is clearly seen in figure 5. Under these conditions, airway overdistension and rupture might occur.

This study showed that x-ray stereophotogrammetry allowed precise measurements of tracheal volumes. The method might be useful in different clinical situations in which changes of the geometry of the trachea would be of interest. From measurements of tracheal volume at varying ventilatory settings, it also appeared that overdistension of the airway occurred at $P_T'$ greater than 3.0 kPa, and at PEEP of more than 1.0 kPa. The relationship between abdominal pressure and airway mechanics was also emphasized.

ACKNOWLEDGEMENT

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### REFERENCES

Arborelius, M. jr, and Lindahl, S. (1980). Dynamic behaviour of the chest and of the abdomen in anaesthetized piglets during rapid insufflation. *Br. J. Anaesth.*, **52**, 5.

Aronson, A. S., Hansson, L. I., and Selvik, G. (1978). Roentgen stereophotogrammetry for determination of daily longitudinal bone growth in the rabbit. *Acta Radiolog. Diagn.*, **19**, 97.

Bickerman, H. A., Beck, G. J., Gordon, C., and Barach, A. L. (1952). Physical methods of simulating mechanisms of human cough: elimination of radiopaque material from bronchi of dogs. *J. Appl. Physiol.*, **5**, 92.

Claesson, G., Fredlund, P., Mühlow, A., and Selvik, G. (1978). Roentgen stereophotogrammetry for evaluation of liver volume and shape. *Acta Radiol. Diagn.*, **19**, 423.

Fraser, R. G. (1961). Measurements of the caliber of human bronchi in three phases of respiration by cinebronchography. *J. Can. Assoc. Radiol.*, **12**, 102.

Gayrard, P., Leonardelli, M., and Noirclere, M. (1969). Effets de l'inflation pulmonaire sur les diamètres bronchiques chez le chien. *Bull. Physio-Pathol. Resp.*, **5**, 465.

Hahn, H. L., Graf, P. D., and Nadel, J. A. (1976). Effect of vagal tone on airways diameters and on lung volume in anaesthetized dogs. *J. Appl. Physiol.*, **41**, 581.

Hughes, J.M.B., Hoppin, F. G. jr, and Mead, J. (1972). Effect of lung inflation on bronchial length and diameter in excised lungs. *J. Appl. Physiol.*, **32**, 25.

Lindahl, S., and Okmian, L. (1979). Experimental studies on artificial ventilation using a tidal volume ventilator. Mechanics and dynamics of ventilation. *Acta Anaesthesiol. Scand.*, **23**, 359.

Macklin, C. L. (1932). Dynamic bronchial tree. *Am. Rev. Tuberc.*, **25**, 393.

Martin, H. B., and Proctor, D. F. (1958). Pressure–volume measurements on dog bronchi. *J. Appl. Physiol.*, **13**, 337.

Ovenfors, C. O. (1964). Pulmonary interstitial emphysema. *Acta Radiol.* (Suppl.), **224**.

Rune, B., Jacobsson, S., Sarnäs, K.-V., and Selvik, G. (1979). A roentgen stereophotogrammetric study of implant stability and movement of segments in the maxilla of infants with cleft lip and palate. *Cleft Palate J.*, **16**, 267.

Selvik, G. (1974). A roentgen stereophotogrammetric method for the study of the kinematics of the skeletal system. Thesis. AV-centralen, Lund, Sweden.

Tropé, C., Selvik, G., Kullander, S., Mattsson, W., Mühlow, A., and Åstedt, B. (1978). Antineoplastic-drug effect evaluated with a new X-ray stereophotographic measurement of the tumour volume. *Ann. Chir. Gynaecol.*, **67**, 82.

## ESTIMATION PAR STEREOPHOTOGRAMMETRIE DU VOLUME DE LA TRACHEE CHEZ LE LAPIN

### RESUME

Après mise en place de billes de tantale dans la paroi trachéale de lapins, on a étudié s'il était possible et précis d'utiliser la stéréophotogrammétrie pour étudier les volumes des voies aériennes. On a mesuré les modifications du volume trachéal en fonction des différentes modalités de ventilation au cours de l'anesthésie et de la ventilation artificielle. La précision de la méthode est élevée et même les faibles modifications de volume induites par un changement de fréquence respiratoire à ventilation alvéolaire constante ont été détectées. Le volume trachéal était maximum pour des pressions positives de fin d'expiration de plus de 1,0 kPa et pour des préssions trachéales de fin d'expiration supérieures à 3,0 kPa. L'absence d'augmentation ultérieure des volumes trachéaux à des pressions plus élevées pourrait être liée aux propriétés élastiques des voies aériennes. La stéréophotogrammétrie aux rayons X permet des mesures précises des volumes trachéaux et la méthode pourrait être utile dans des situations cliniques où l'étude des modifications du volume trachéal présente un intérêt.

## STEREOPHOTOGRAPHISCHE BERECHNUNG DER TRACHEALVOLUMINA BEIM KANINCHEN

### ZUSAMMENFASSUNG

Nach Einführen von Tantal-Bällen in die Trachealwand von Kaninchen wurde die Durchführbarkeit und die Genauigkeit der Röntgenstereophotometrie für die Untersuchung der Volumina der Luftwege untersucht. Veränderungen des Trachealvolumens bei verschiedener Anordnung der Beatmungsgeräte während Narkose und künstlicher Beatmung wurden gemessen. Die Genauigkeit der Methode war groß und sogar kleine Volumenänderungen, hervorgerufen durch verschiedene Beatmungsfrequenzen bei unveränderter alveolärer Belüftung, wurden entdeckt. Das Trachealvolumen war am größten bei PEP von mehr als 1,0 kPa und endexpiratorischen Trachealdrücken von über 3,0 kPa. Daß das Trachealvolumen bei höheren Drücken nicht größer war, mag durch die Elastizität der Luftwege bedingt sein. Die Röntgenstereophotometrie erlaubt genaue Messungen des Trachealvolumens und die Methode könnte in klinischen Situationen nützlich sein, in denen Veränderungen des Trachealvolumens von Interesse sind.

## EVALUACION ETEREOFOTOGRAMETRICA DE LOS VOLUMEN TRAQUEALES DEL CONEJO

### SUMARIO

Se investigaron la viabilidad y la precisión de la etereofotogrametría para llevar a cabo estudios de los volúmenes de la tráquea, después de la inserción de bolas de tántalo en las paredes traqueales de conejos. Se evaluaron los cambios en el volumen traqueal durante la anestesia y la ventilación artificial, a diferentes establecimientos del ventilador. El método demostró ser de una gran precisión e incluso detectó pequeños cambios en el volumen, ocasionados por diferentes frecuencias de ventilación bajo una ventilación alveolar constante. El volumen traqueal fue máximo a las presiones expiratorias terminales de carácter positivo, superiores a 1,0 kPa y a presiones traqueales inspiratorias de carácter terminal que fueran superiores a 3,0 kPa. El que los volúmenes traqueales no aumentaran bajo condiciones de alta presión puede que sea causa de las propiedades elásticas de las tráqueas. La etereofotogrametría por rayos X permite la medición precisa de los volúmenes traqueales, por lo que el método puede ser útil en aquellas situaciones clínicas en que los cambios de los volumenes traqueales sean de interés.

*Br. J. Anaesth.* (1982), 54, 1003

# A HAEMORHEOLOGICAL STUDY OF ALTHESIN

J. E. ORR, R. J. L. DAVIDSON, I. F. RUSSELL AND G. S. ROBERTSON

## SUMMARY

In 11 patients, induction of anaesthesia with a slow i.v. infusion of Althesin caused small but statistically significant reductions in venous haematocrit and plasma viscosity. Whole blood viscosity was slightly reduced but this only attained statistical significance at one ($0.945\,s^{-1}$) of several shear rates tested. Red cell deformability remained unchanged. *In vitro* studies revealed that when dilutional effects were eliminated, plasma viscosity was not reduced by the addition of cremophor or Althesin to plasma. The small reductions in haematocrit and plasma viscosity observed *in vivo* are considered to be secondary effects of sedation.

Gramstad and Stovner (1979) reported major reductions in plasma viscosity after the addition of cremophor-containing anaesthetic agents both *in vivo* and *in vitro*. Plasma viscosity is largely dependent on the plasma concentrations of $\alpha$ and $\beta$ globulins, and to a lesser extent on the fibrinogen and albumin content. Plasma depleted of fibrinogen behaves as a Newtonian fluid and therefore does not exhibit shear rate dependence. Thus, when determining plasma viscosity it is not necessary to measure it at different shear rates (Merill et al., 1963; Wells et al., 1963). In contrast, whole blood is a non-Newtonian fluid—the ratio of shear stress to shear rate is not constant and therefore its viscosity must be measured at various shear rates (Dintenfass, 1962). Blood flow in larger vessels and arterioles is influenced by whole blood viscosity, which in turn is related to the total plasma protein and red cell concentration (haematocrit), aggregation and deformability. All these indices were therefore included for measurement.

This communication reports the haemorheological findings in 11 patients in whom anaesthesia was induced with an i.v. Althesin infusion, and our observations of the *in vitro* effects of cremophor and Althesin on plasma viscosity.

## PATIENTS AND METHODS

### In vivo *study*

Eleven healthy patients (ASA grade 1; eight male, three female; mean age 34.5 yr), undergoing minor elective surgery gave consent for the study. No premedication was given. Anaesthesia was induced by continuous i.v. infusion of Althesin ($0.5\,ml\,min^{-1}$) until the lash reflex disappeared and was maintained by a reduced infusion rate ($0.166\,ml\,min^{-1}$), the patients breathing air throughout the study. Venous blood samples were obtained before induction and 5–10 min after the loss of the lash reflex, but before surgery commenced. All laboratory determinations were performed within 1 h of venepuncture and comprised: routine haematological assessment of peripheral blood including platelet count (Coulter Counter Model S plus); plasma viscosity determined in duplicate at 25 °C (Coulter Harkness capillary viscometer); whole blood viscosity measured in duplicate by a Contraves Low Shear 30 viscometer at 37 °C and at four shear rates ($0.11, 0.945, 11.02, 94.5\,s^{-1}$) with correction to a standard haematocrit of 0.45 (Dormandy, 1970); red cell deformability measured by a filtration method (Reid et al., 1976) using a negative pressure of 20 cm $H_2O$ and nucleopore membranes (pore size $5\,\mu m$).

The results were analysed using the paired *t* test, and a probability of $< 0.05$ was taken as significant.

### In vitro *study*

This involved three separate experiments. All plasma viscosities were measured in quadruplicate at 25 °C using a Coulter Harkness capillary viscometer calibrated for linearity using pooled plasma. The

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results for pooled plasma were compared with those of the test samples.

*Experiment 1.* In order to assess the effect of dilution on plasma viscosity, three different plasma/Althesin dilutions were prepared while maintaining the concentration of alphaxalone constant at 18 μg ml$^{-1}$ in all three dilutions. Thus Althesin was diluted 1 : 50 with 0.9% saline and 0.2 ml of this was added to 1.8 ml of plasma (Gramstad and Stovner, 1979), resulting in a 1 : 10 plasma dilution. A 1 : 100 plasma dilution vas prepared by diluting Althesin 1 : 5 with 0.9% saline and adding 0.02 ml of this to 1.98 ml of plasma. By adding 0.01 ml of Althesin to 4.99 ml of plasma, a 1 : 500 plasma dilution was prepared.

*Experiment 2.* This was devised to assess any effect of different concentrations of alphaxalone on plasma viscosity while maintaining plasma dilution constant (1 : 100). A concentration of alphaxalone 18 μg ml$^{-1}$ was prepared by adding 0.02 ml of a 1 : 5 dilution of Althesin to 1.98 ml of plasma. By diluting Althesin 1 : 10 with 0.9% saline and adding 0.02 ml of this to 1.98 ml of plasma, a concentration of 9 μg ml$^{-1}$ of alphaxalone was prepared. A concentration of alphaxalone 3 μg ml$^{-1}$ was prepared by diluting Althesin 1 : 30 with 0.9% saline and adding 0.02 ml of this to 1.98 ml of plasma. This concentration of alphaxalone was selected as it was considered to be similar to plasma concentrations obtaining in Althesin anaesthesia (Sear and Prys-Roberts, 1979).

*Experiment 3.* In order to determine the effect of cremophor EL alone on plasma viscosity, two plasma dilutions were studied. To 1.8 ml of plasma was added 0.2 ml of a 1 : 250 dilution of cremophor EL in 0.9% saline, producing a plasma dilution of 1 : 10 (Gramstad and Stovner, 1979); 0.02 ml of a 1 : 25 dilution of cremophor EL was added to 1.98 ml of plasma, producing a plasma dilution of 1 : 100.

When analysing the results of the *in vitro* study, a difference of more than 2 standard deviations from the mean of the pooled plasma viscosity was taken as being significant ($P < 0.05$).

## RESULTS

### In vivo *study*

The dose of Althesin required to induce anaesthesia varied from 2 to 10 ml (mean 4.6 ml) and the total dose administered before sampling ranged from 3 to 15.5 ml (mean 6.8 ml) given over periods of 7–19 min.

The resting peripheral blood haematological assessment was normal in all subjects. After administration of Althesin the only alteration was a small but significant ($P < 0.01$) reduction in haematocrit (table I).

Plasma viscosity showed a mean decrease of 4% ($P < 0.01$) after administration of Althesin (table I).

Although the mean value for whole blood viscosity was reduced after Althesin at all four shear rates, only the reduction at 0.945 s$^{-1}$ attained statistical significance ($P < 0.05 > 0.02$).

Red cell deformability was not significantly changed after administration of Althesin.

### In vitro *study*

*Experiment 1.* Only with the 1 : 10 plasma dilution was there significant reduction in plasma viscosity compared with the pooled plasma ($P < 0.05$). Alphaxalone 18 μg ml$^{-1}$ had no significant effect on plasma viscosity when the plasma dilution was 1 : 100 and 1 : 500 (table II).

*Experiment 2.* Differing concentrations of alphaxalone at a 1 : 100 plasma dilution had no effect on plasma viscosity (table III).

TABLE I. *Means of values (±SD) for haematocrit, plasma and whole blood viscosities in 11 patients before and after administration of Althesin.* *P < *0.05, paired* t *test. cp = centipoise*

| | | Before Althesin | After Althesin |
|---|---|---|---|
| Haematocrit | | 0.456 (±0.040) | 0.436 (±0.34)* |
| Plasma viscosity (cp) | | 1.75 (±0.10) | 1.68 (±0.08)* |
| Whole blood viscosity (cp) | | | |
| Shear rate (s$^{-1}$): | 0.110 | 43.9 (±6.9) | 42.9 (±5.6) |
| | 0.945 | 18.9 (±1.7) | 17.5 (±1.7)* |
| | 11.02 | 7.4 (±0.8) | 7.0 (±0.6) |
| | 94.5 | 4.5 (±0.5) | 4.4 (±0.5) |

TABLE II. *Plasma viscosity of different plasma dilutions (mean ± 2SD); alphaxalone concentration constant (18 μg ml$^{-1}$).* *P < *0.05*

| Sample | Plasma viscosity (cp) |
|---|---|
| Pooled plasma | 1.78 ± 0.04 |
| Plasma dilution 1:10 | 1.70* |
| Plasma dilution 1:100 | 1.82 |
| Plasma dilution 1:500 | 1.82 |

TABLE III. *Plasma viscosity of different concentrations of alphaxalone (mean* ± 2SD)*; plasma dilution constant (1:100)*

| Alphaxalone concn in pooled plasma (μg ml$^{-1}$) | Plasma viscocity (cp) |
|---|---|
| 0 | 1.87 ± 0.04 |
| 18 | 1.86 |
| 9 | 1.87 |
| 3 | 1.89 |

*Experiment 3.* The addition of cremophor EL to pooled plasma at a 1:10 plasma dilution caused a significant reduction of plasma viscosity ($P < 0.05$). No significant effect was seen when the same concentration of cremophor was prepared at a 1:100 plasma dilution (table IV).

TABLE IV. *Plasma viscosity of different plasma dilutions (mean ± 2SD); cremophor concentration constant (1:250).* *P < 0.05*

| Sample | Plasma viscosity (cp) |
|---|---|
| Pooled plasma | 1.90 ± 0.04 |
| Plasma dilution 1:10 | 1.76* |
| Plasma dilution 1:100 | 1.94 |

## DISCUSSION

In the present study, significant reductions in venous haematocrit and plasma viscosity were found after administration of Althesin. Similar changes in haematocrit and plasma viscosity have been reported after the onset of electrical sleep (Magora, Hershko and Aronson, 1970) and the administration of droperidol (Aronson, Magora and London, 1970). In both instances these changes were attributed to the effects of sedation and a reduction in sympathetic nervous activity, possibly leading to a redistribution of extracellular fluid from the extravascular to the intravascular compartment. This explanation is supported by the converse effect of increased sympathetic stimulation leading to reduced plasma volume and haemoconcentration (Kaltreider and Meneely, 1940; Kaltreider, Meneely and Allen, 1942; Cohn, 1966). In the present *in vivo* study, all measurements were made before the onset of surgical stimulation in order to avoid possible effects of surgical stress.

The modest reduction in plasma viscosity (4%) recorded in our study differs markedly from that reported by Gramstad and Stovner (1979), who found a 42% reduction in plasma viscosity *in vivo* after the induction of anaesthesia with cremophor-containing anaesthetic agents, including Althesin. Similarly they demonstrated a 45% reduction in plasma viscosity *in vitro* after the addition of cremophor-containing anaesthetic agents and cremophor alone to pooled plasma. These authors used the Wells–Brookfield cone-in-plate viscometer which is recognized to be inaccurate at low shear rates (Rand and Lacombe, 1964; Gordon and Ravin, 1978) and it therefore seems pertinent that the major reductions in plasma viscosity reported by them were found only when measured at these low shear rates ($11.5\,s^{-1}$). Although we found small reductions in whole blood viscosity at all four shear rates, only the reduction observed at $0.945\,s^{-1}$ was statistically significant. The Contraves Low Shear viscometer is of the coaxial cylinder type and is known to be accurate at low shear rates (Dodds, 1979).

The importance of measuring blood viscosity at low shear rates has been stressed in determining the thixotropic properties of blood (Dintenfass, 1962). It has also been proposed that the physiological range of shear rates (those at which measurements should be made in order to be clinically relevant) should encompass the higher shear rates (Dormandy, 1970). At these higher rates, Gramstad and Stovner did not find major reductions in plasma viscosity after the administration of cremophor-containing anaesthetic agents. They claimed further that the *in vivo* reduction in plasma viscosity lasted for 50 min but they only reported viscosity values measured at a shear rate of $11.5\,s^{-1}$.

Our *in vitro* studies would appear to indicate that Althesin and cremophor do not cause a significant reduction in plasma viscosity when any dilution effect is eliminated. Isotonic dilution has been shown to depress both plasma and whole blood viscosity (Rand and Lacombe, 1964). Our investigation has clearly shown that a 1:10 plasma dilution will cause a reduction in plasma viscosity and this was the only dilution used by Gramstad and Stovner in their *in vitro* study.

In conclusion, the results of our studies do not support the view that the administration of cremophor-containing anaesthetic agents is associated with a substantial reduction in plasma viscosity. Any minor reductions may be attributable to the secondary effects of sedation.

## ACKNOWLEDGEMENTS

The authors wish to thank Glaxo Laboratories Ltd for supplying cremophor EL, Mr James Brown A.I.M.L.S. for invaluable technical assistance, and Mr James Kyle for his co-operation in allowing us to study patients under his clinical care.

## REFERENCES

Aronson, H. B., Magora, F., and London, M. (1970). The influence of droperidol on blood viscosity in man. *Br. J. Anaesth.*, 42, 1089.

Cohn, J. N. (1966). Relationship of plasma volume changes to resistance and capacitance vessel effects of sympathomimetic amines and angiotensin in man. *Clin. Sci.*, 30, 267.

Dintenfass, L. (1962). Thixotropy of blood and proneness to thrombus formation. *Circ. Res.*, 11, 233.

Dodds, A. J. (1979). Apparatus for measuring blood viscosity. *Br. J. Clin. Equip.*, 4, 224.

Dormandy, J. A. (1970). Clinical significance of blood viscosity. *Ann. R. Coll. Surg. Engl.*, **47**, 211.

Gordon, R. J., and Ravin, M. B. (1978). Rheology and anesthesiology. *Anesth. Analg. (Cleve.)*, **55**, 244.

Gramstad, L., and Stovner, J. (1979). Plasma viscosity and cremophor-containing anaesthetics. *Br. J. Anaesth.*, **51**, 1175.

Kaltreider, N. L., and Meneely, G. R. (1940). The effect of exercise on the volume of the blood. *J. Clin. Invest.*, **19**, 627.

—— —— Allen, J. R. (1942). The effect of epinephrine on the volume of the blood. *J. Clin. Invest.*, **21**, 339.

Magora, F., Hershko, C., and Aronson, H. B. (1970). The effect of electrical sleep on the viscosity of the blood. *Br. J. Anaesth.*, **42**, 1085.

Merrill, E. W., Cokelet, G. C., Britten, A., and Wells, R. E. (1963). Non-Newtonian rheology of human blood—effect of fibrinogen deducted by subtraction. *Circ. Res.*, **13**, 48.

Rand, P. W., and Lacombe, E. (1964). Haemodilution, tonicity, and blood viscosity. *J. Clin. Invest.*, **43**, 2214.

Reid, H. L., Bannesh, J., Lock, P. J., Dormandy, J. A., and Dormandy, T. L. (1976). A simple method for measuring erythrocyte deformability. *J. Clin. Pathol.*, **29**, 855.

Sear, J. W., and Prys-Roberts, C. (1979). Plasma concentrations of alphaxalone during continuous infusion of Althesin. *Br. J. Anaesth.*, **51**, 861.

Wells, R. E., Perera, R. D., Gawronski, T., and Shahriari, A. A. (1963). Effects of plasma proteins upon the rheological character of blood in the microcirculation (abstract). *J. Clin. Invest.*, **42**, 991.

## UNE ETUDE HEMORHEOLOGIQUE DE L'ALTHESIN

### RESUME

Chez 11 patients, l'induction de l'anesthésie par une perfusion i.v. lente d'Althésin a entraîné une diminution faible mais statistiquement significative de l'hématocrite veineux et de la viscosité plasmatique. La viscosité sanguine globale était légèrement abaissée mais ceci n'était statistiquement significatif que pour l'une (0,945 s$^{-1}$) des diverses vitesses testées. La déformabilité des globules rouges demeurait inchangée. Des études *in vitro* ont montré qu'une fois les effets de dilution éliminés, la viscosité du plasma n'était pas réduite par l'addition de crémophore ou d'Althésin au plasma. Les faibles réductions de l'hématocrite et de la viscosité du plasma observées *in vivo* sont considérées comme secondaires à la sédation.

## EINE HAEMATOLOGISCHE UNTERSUCHUNG ÜBER ALTHESIN

### ZUSAMMENFASSUNG

Bei 11 Patienten verursachte die Narkoseeinleitung mit einer langsamen i.v. Infusion von Althesin eine kleine, statistisch jedoch signifikante Verminderung des venösen Hämatokrit und der Plasmaviskosität. Die gesamt Blutviskosität selber war leicht vermindert, wobei sie allerdings nur in einer einzigen Probe aus verschiedenen Testreihen statistische Bedeutung erlangte. Die Verformbarkeit der Roten Blutzellen blieb unverändert. *In vitro* Untersuchungen zeigten, daß—sobald Verdünnungseffekte ausgeschlossen—die Plasmaviskosität durch die zusätzliche Gabe von Cremophor oder Althesin zum Plasma nicht vermindert wurde. Die geringe Abnahme des Hämatokrits und der Plasmaviscosität, *in vivo* beobachtet, werden als Nebeneffekt durch die Sedierung angesehen.

## UN ESTUDIO HEMORHEOLOGICO DE LA ALTESINA

### SUMARIO

La inducción de anestesia en 11 pacientes, mediante una infusión intravenosa de altesina de carácter lento, ocasionó reducciones pequeñas, pero de importancia esadística, en la viscosidad del plasma y en la hemocríta venosa. La viscosidad sanguínea total se redujo ligeramente pero esto alcanzó importancia estadística en tan sólo uno (0,945 seg.$^{-1}$) de los diversos regímenes verificados. La capacidad de deformación de los glóbulos rojos no sufrió cambio alguno. Los estudios *in vitro* revelaron que cuando los efectos de dilución se eliminaron, la viscosidad del plasma no se redujo por la adición al plasma de cromofor ni de altesina. La ligera reducción de la viscosidad hematocrita y del plasma observada *in vivo* se consideran como efectos secundarios de la anestesia.

*Br. J. Anaesth.* (1982), 54, 1007

# CORRESPONDENCE

## TOCOLYSIS AND ANAESTHESIA FOR CAESAREAN SECTION

Sir,—Beta-mimetics are used with increasing frequency as tocolytic agents in obstetrics, and despite claims to greater selectivity for their uterine effects these compounds share the same side-effects—tachycardia, hypotension and uterine atony. These side-effects and their consequences were examined in a comparative retrospective study involving 23 patients treated with buphenine (average 0.3 mg min$^{-1}$ for a 60-kg patient) and 23 control patients, all undergoing Caesarean section with a standard anaesthetic technique (thiopentone–suxamethonium induction, maintenance with 35% nitrous oxide in oxygen with 0.2% methoxyflurane or 0.5% halothane, analgesia only after delivery with pentazocine or pethidine, syntocinon 5 mg i.v. and 10 mg infusion).

Patients receiving tocolysis (fig. 1) had a consistently faster resting heart rate before induction (mean 132 *v.* 98 beat min$^{-1}$), reaching an average maximum of 134 *v.* 118 in the indection–delivery interval, before analgesics were administered, while the slowest average heart rate was 103 *v.* 87. The heart rate response to surgical stress was strikingly reduced in the tocolysis series, as was the tachycardic response to syntocinon given after delivery (increase of 2.7% *v.* 13.3% to surgical stress, and of 1.6% *v.* 7.2% to syntocinon). Overall this led to a "fixed fast heart rate" associated with tocolysis. The variability of the heart rate as assessed by an index (average standard deviation as % of the mean value) was only half that of the controls (7.6 *v.* 15). By contrast, systolic and diastolic pressures showed little difference between the two groups.

The practical implication of these findings is, first, that the usual signs of inadequate analgesia and of hypovolaemia are obtunded under tocolysis. The fixed fast heart rate may be taken as a sign of inadequate analgesia and result in an overdosage of analgesics; that this risk is real is shown by the fact that on average the patients under tocolysis received more analgesics (0.5 mg kg$^{-1}$ *v.* 0.31 mg kg$^{-1}$ of pentazocine).

A second possible danger is the wrong estimation of blood loss, the tachycardia being interpreted as a sign of hypovolaemia. In the series reported here, although the anaesthetist had no special awareness of these problems at the time, the volumes of i.v. fluids and of blood given during the operation were not significantly different in the two series.

Finally, another risk is obviously that of uterine atony. Perhaps surprisingly, this did not create any problem in these patients, as again confirmed by the volumes of i.v. fluids and blood received. This may be because of the systematic use of syntocinon immediately after delivery.

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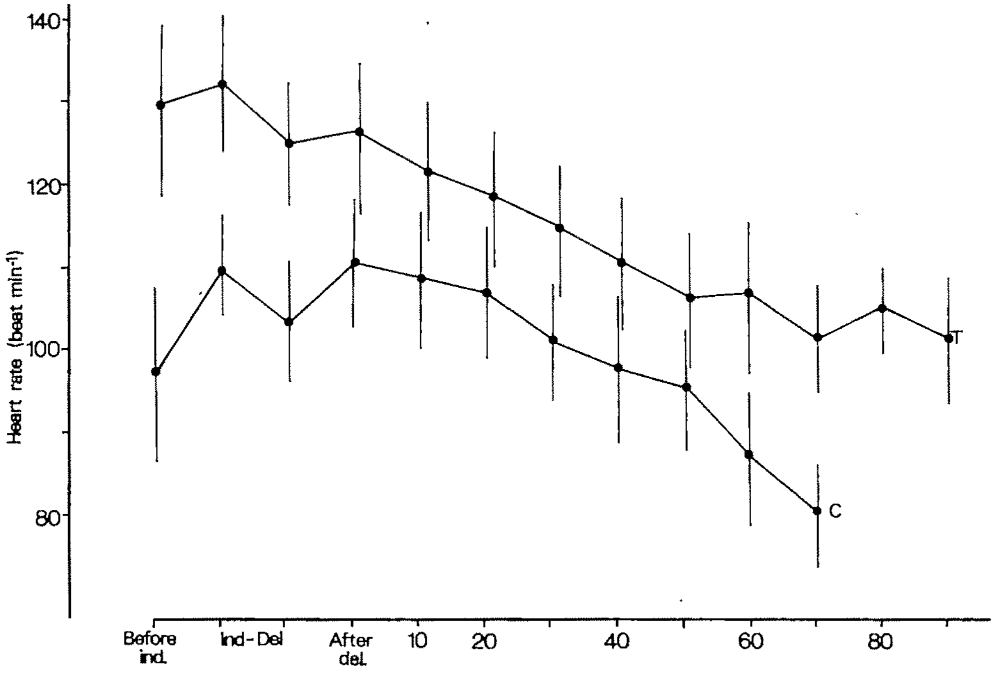

FIG. 1. Heart rates during operation in patients under tocolysis (T) and in the control series (C). Ind. = induction; del. = delivery.

*Br. J. Anaesth.* (1982), 54, 1009

# BOOK REVIEWS

*Chest Physiotherapy in the Intensive Care Unit.* Edited by C. F. Mackenzie, N. Ciesla, C. Imle and N. Klemic. Published by Williams & Wilkins, Baltimore. Pp. 260; illustrated; indexed. Price $27.00.

This densely-written treatise describes with enthusiastic detail the attitudes, practices and results of chest physiotherapy in the 30-bed Intensive Care Area within an American Trauma Unit. As is made very clear, the patient population is dominated by young male accident victims, although these multiply-injured patients illustrate adequately the full range of problems likely to be encountered in a general I.T.U.

The chapters may be divided into two types and may tend to appeal to different sets of readers. The first comprise those contributed by Dr Mackenzie and are aimed at the "medical" side of the I.T.U. team, while the second are written by the three physiotherapists and are likely to be of more interest to their fellow professionals and to the nursing staff in the I.T.U.

Dr Mackenzie describes the history of chest physiotherapy and considers the clinical indications for its use. He reviews some physiological changes associated with and following its use, contributing data on blood-gas, pulmonary mechanics and radiological changes which confirm the difficulties in investigating and assessing the value of the various treatments. There are quibbles; I found the use of the physiologically meaningless $Pa_{O_2}/FI_{O_2}$ index unhelpful—(what is wrong with the alveolar and arterial tension difference or the venous admixture?)—and the explanation for the apparent decrease in cardiac output following physiotherapy (p. 144) unconvincing. The table which summarizes the less desirable effects and hence limitations of chest physiotherapy is particularly useful, as are the comments on the two conferences on the scientific basis of respiratory therapy.

In the physiotherapists' chapters, there are good descriptions of the physiological mechanisms involved in the clearance of secretions from the lungs, but the methods described include only a selection of those which could be included under chest physiotherapy. Although other methods are discussed, they are largely dismissed for what their protagonists will consider inadequate reasons. (Our physiotherapist was quite huffy about their treatment of "huffing"!) I should have been more convinced of the need to position patients in some of the more extreme poses recommended for postural drainage, particularly in view of the possible complications described later in the book, were the scientific evidence for the efficiency of gravity in aiding the removal of secretions not contained in one short paragraph.

Throughout the book illustrations are profuse and generally helpful; each chapter is well referenced and the index is adequate. It is already clear, however, that the binding of the soft-covered review copy will be inadequate for the rigours of the I.T.U. bookshelf.

This is a useful book which should be available in every I.T.U. Its value is twofold: it both educates and stimulates. It will stir up argument and, one hopes, investigation about the chest physiotherapy practices which are in common use and about which there are remarkably few hard data.

*John H. Kerr*

*Lecture Notes on Fluid and Electrolyte Balance.* By Sheila M. Willatts. Published (1982) by Blackwell Scientific Publications, Oxford. Pp. 308; indexed. Price £7.50.

This book is written by a practising anaesthetist with a broad medical background and is aimed to cater for the needs of senior students and junior medical staff. In many ways this is achieved, and the accounts of recent developments and the sections on operative and postoperative fluid regimes are excellent. The first part of the book deals with the physiology of the body fluids and electrolytes and the second with their derangements. The sections on calcium, phosphate and magnesium are informed and up-to-date and there is a short account of parenteral nutrition and of practical precedures.

The consistency and accuracy which one expects in a single author book is not always maintained. The minimum urinary osmolality appears on p. 10 as 300 mOsmol $\text{litre}^{-1}$ and the protein content of PPF is given as 1.8%. Figures for total exchangeable Na and K show wide divergence in different sections and surely hydrogen ions and not bicarbonate should appear as typical constituents of gastric juice?

The book deals with a difficult and complex subject, but one essential for any author is to make explicit what is meant by the term "dehydration" if it is to be used. Dr Willatts uses it in Chapter 5 to describe the comparatively rare state of water depletion, but later it is applied to an account of extracellular fluid depletion. This is accompanied by the surprising statement that it should be corrected slowly if associated with hyponatraemia, for fear of causing disequilibrium and deterioration in c.n.s. signs. Such disequilibrium is only likely to occur as a result of over-rapid correction of hypernatraemic states as a result of the formation of "idiogenic osmoles" within the cells of the brain. Stress is laid on the plasma protein concentration as an indication of e.c.f. loss, but the reviewer has very seldom found this to be helpful.

With one exception, no references are given in the text, but there is a short list of books and papers for further reading. It would be useful to have a few key references at the end of each chapter. The index is not very helpful. Searching for an account of the electrolyte losses attendant on mannitol infusions, the reviewer eventually found the relevant heading on p. 284 to be rewarded baldly with the information "Mannitol is one of the osmotic diuretics".

The book is well produced between plastic-faced soft covers.

*P. J. Horsey*

## OTHER BOOKS RECEIVED

*Monographs in Anaesthesiology: Adverse Reactions to Anaesthetic Drugs, 8.* Edited by J. A. Thornton. Published (1981) by Excerpta Medica. Pp. 336; illustrated; indexed. Price $97.00.

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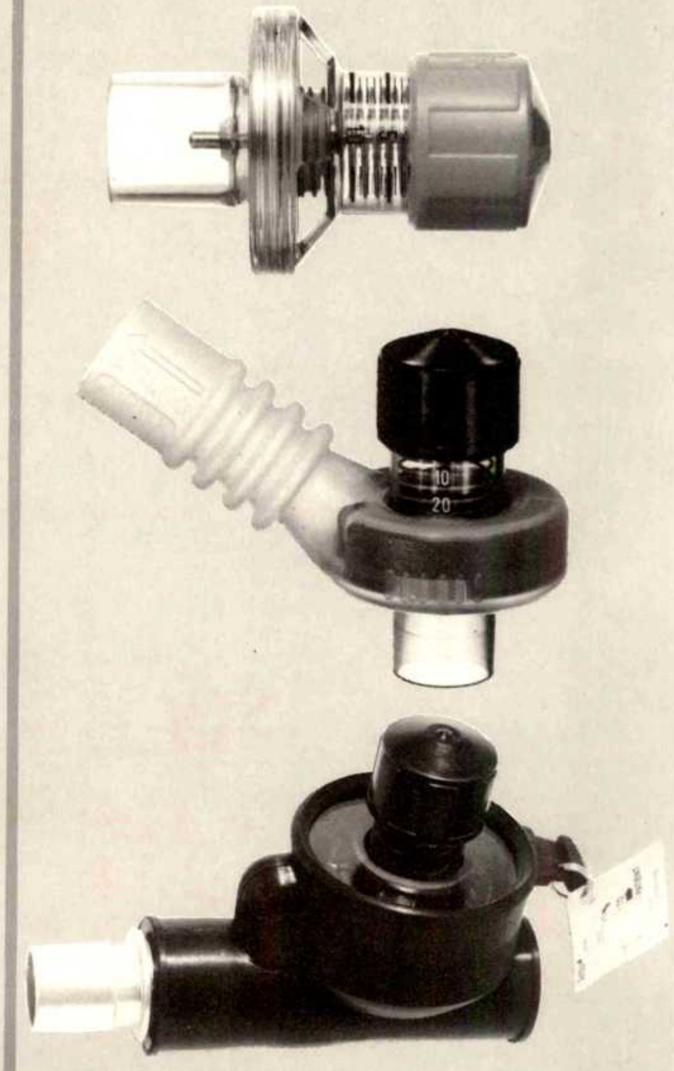

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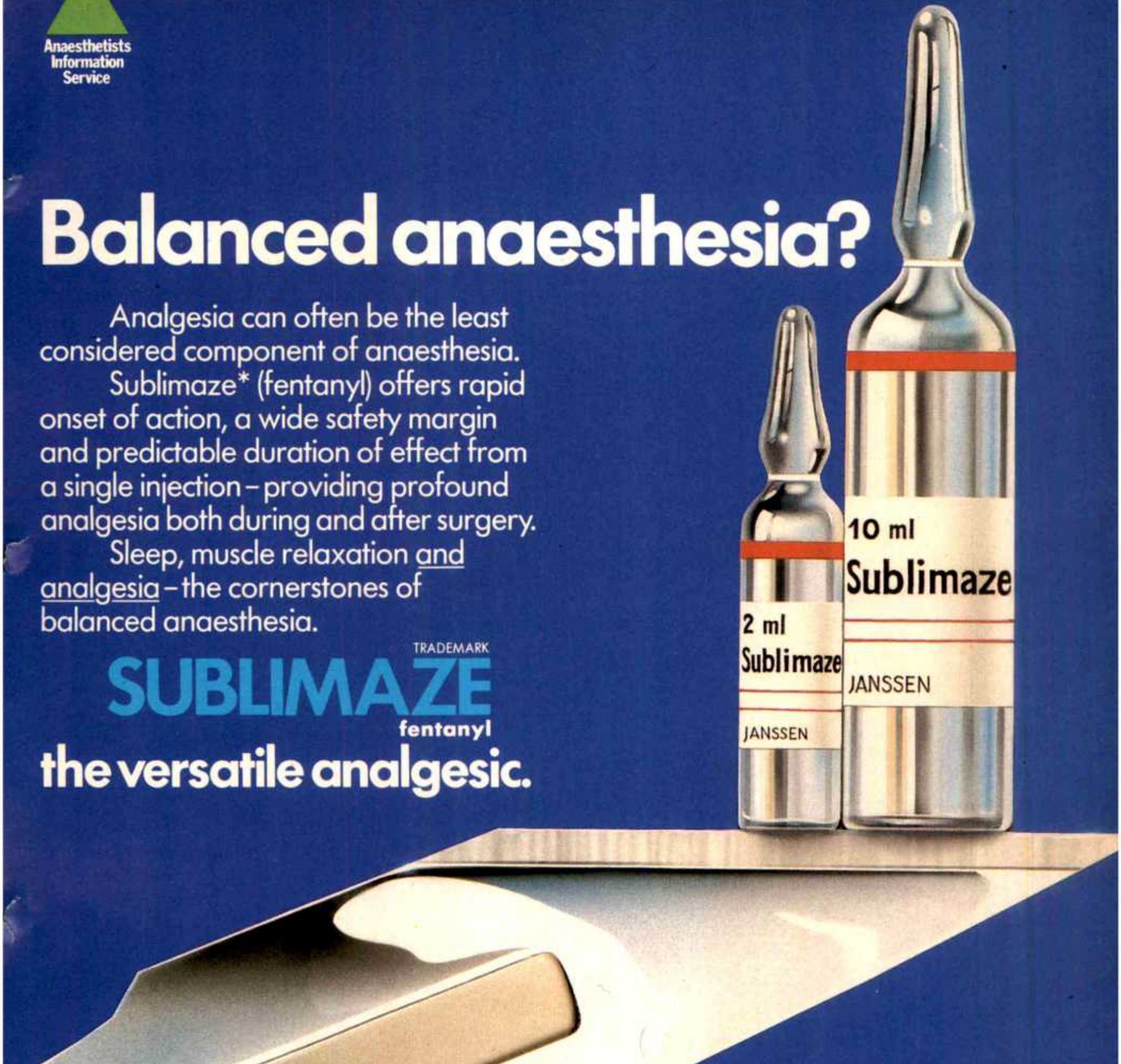

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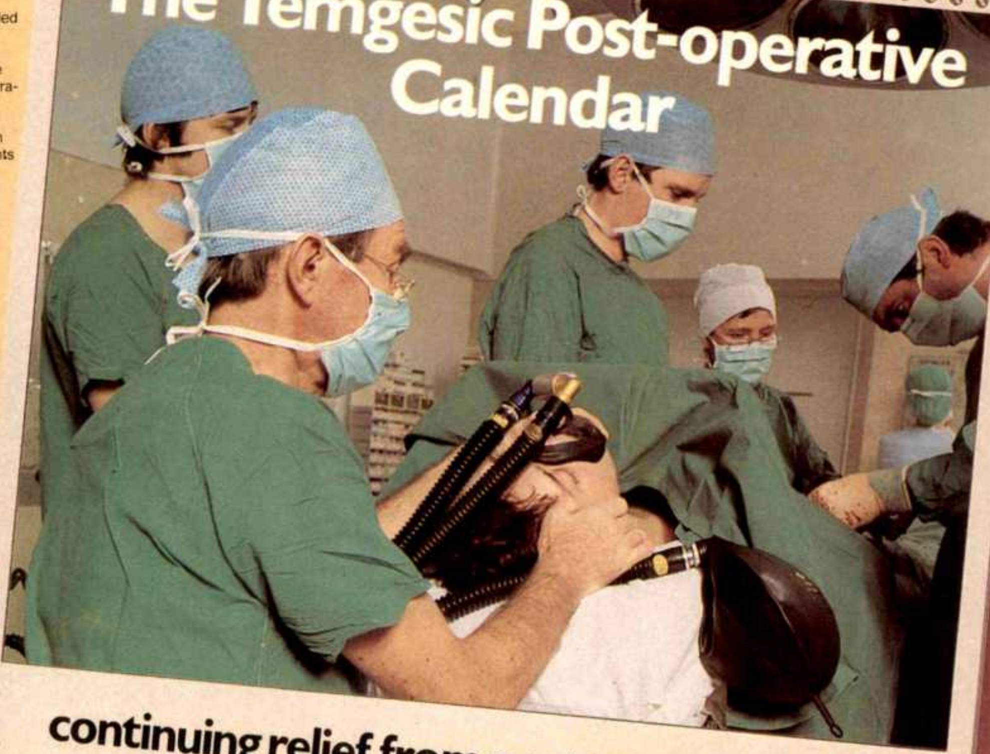

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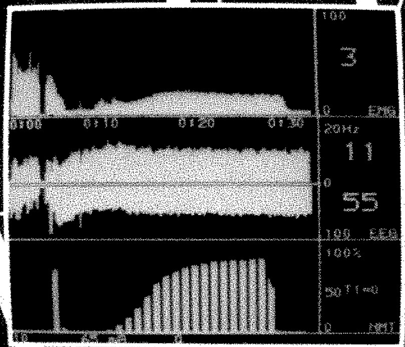

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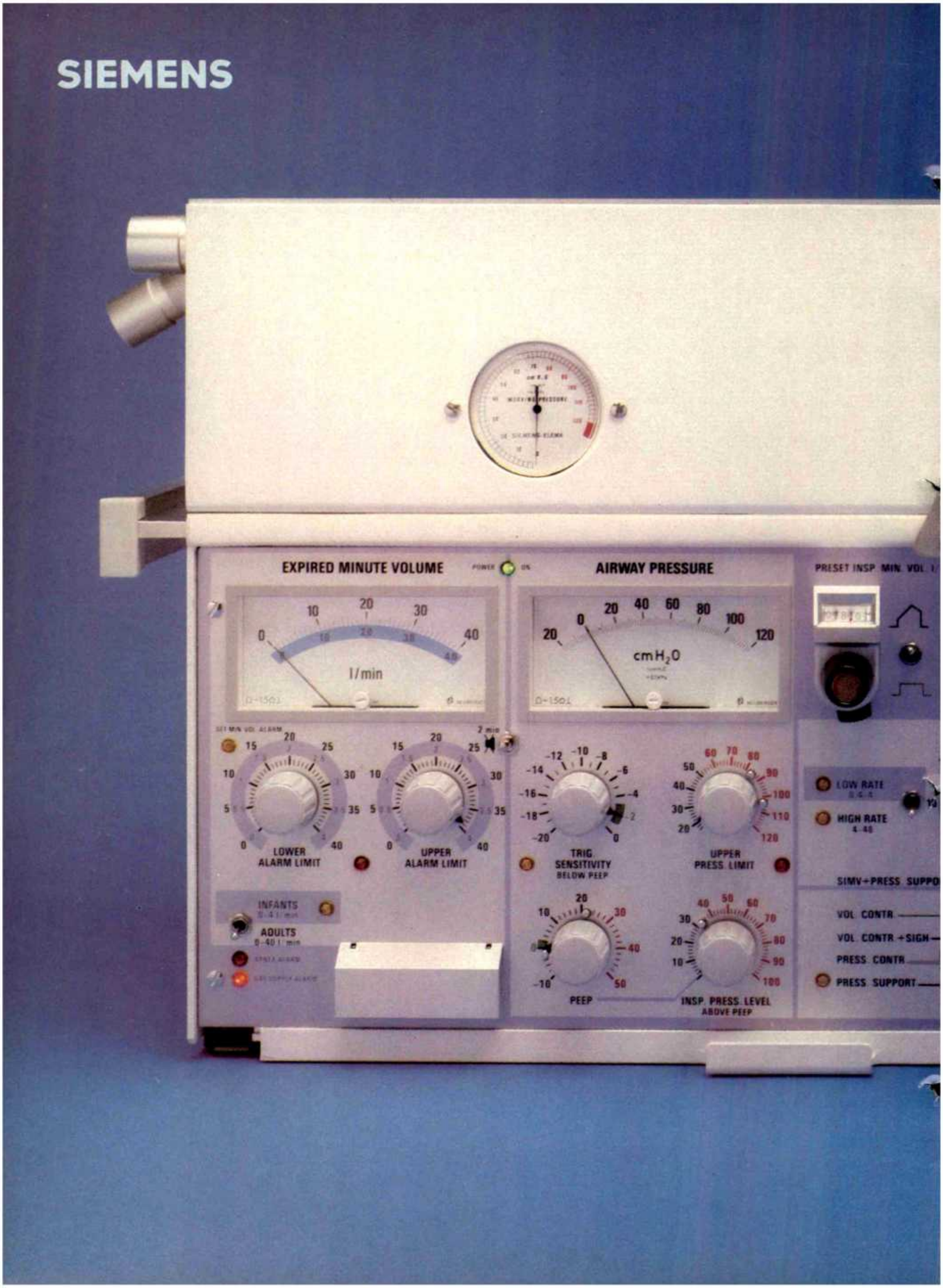
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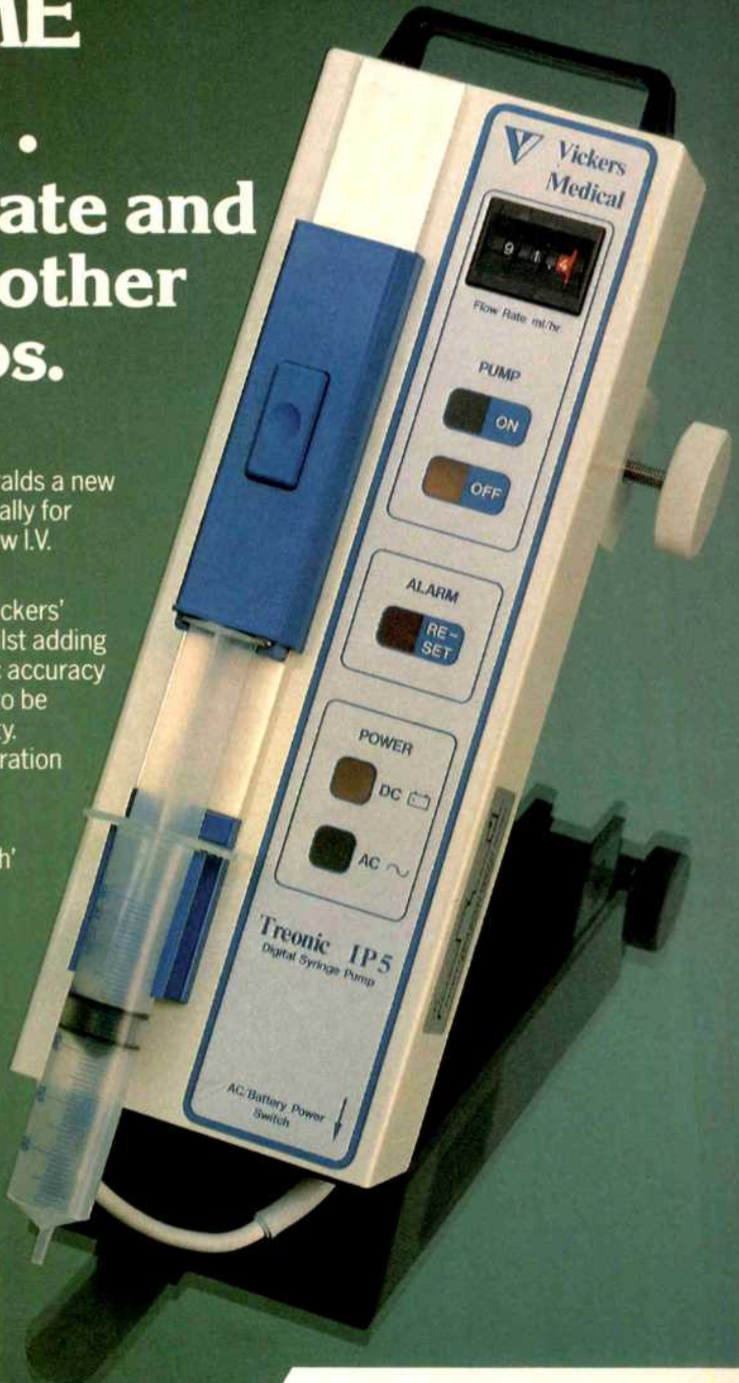

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Photographs should be unmounted glossy prints, and should be protected adequately for mailing. Surfaces should not be marred with clips, pins or by heavy writing on the back. Drawings, charts and graphs should be in black india ink on white paper. Illustrations should be clearly numbered on the back, preferably in soft pencil, with reference to the text, and using arabic numerals. They should be accompanied on a separate sheet by a suitable legend. Lettering should be professional-looking, uniform, preferably in a common typeface, large enough to read at a reduced size, and in proportion to the illustrated material. Lines in the original must also be thick enough to allow for reduction. Magnifications, especially in photomicrographs, should be indicated by a scale on the photograph itself, in order to remain appropriate after reduction. Symbols which are to appear in the legend should be chosen from the following available types:

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2. RESULTS (small capitals)
3. Blood-gas analysis (l.c. roman)
4. *The action of drugs* (italics, centre)
5. *Lung function studies* (italics, full out)
6. *Volume.* Large volumes. . (italics, indent)

*Symbols and Abbreviations.* In accordance with Editorial adoption of SI Units, abbreviations and symbols should follow the conventions described in the booklet "Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors" (ed. G. Ellis), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London, W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

*Spelling, etc.* British spelling should be used with "z" rather than "s" spelling in, e.g. organize, organization.

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It is proposed that a proportion of the Journal be devoted to correspondence each month. Every effort will be made to ensure that correspondence arising from papers in a recent issue is published without delay, and for this reason, relevant correspondence will be given priority over that pertaining to original research. Authors of correspondence concerning original work will receive proofs at the Editor's discretion.

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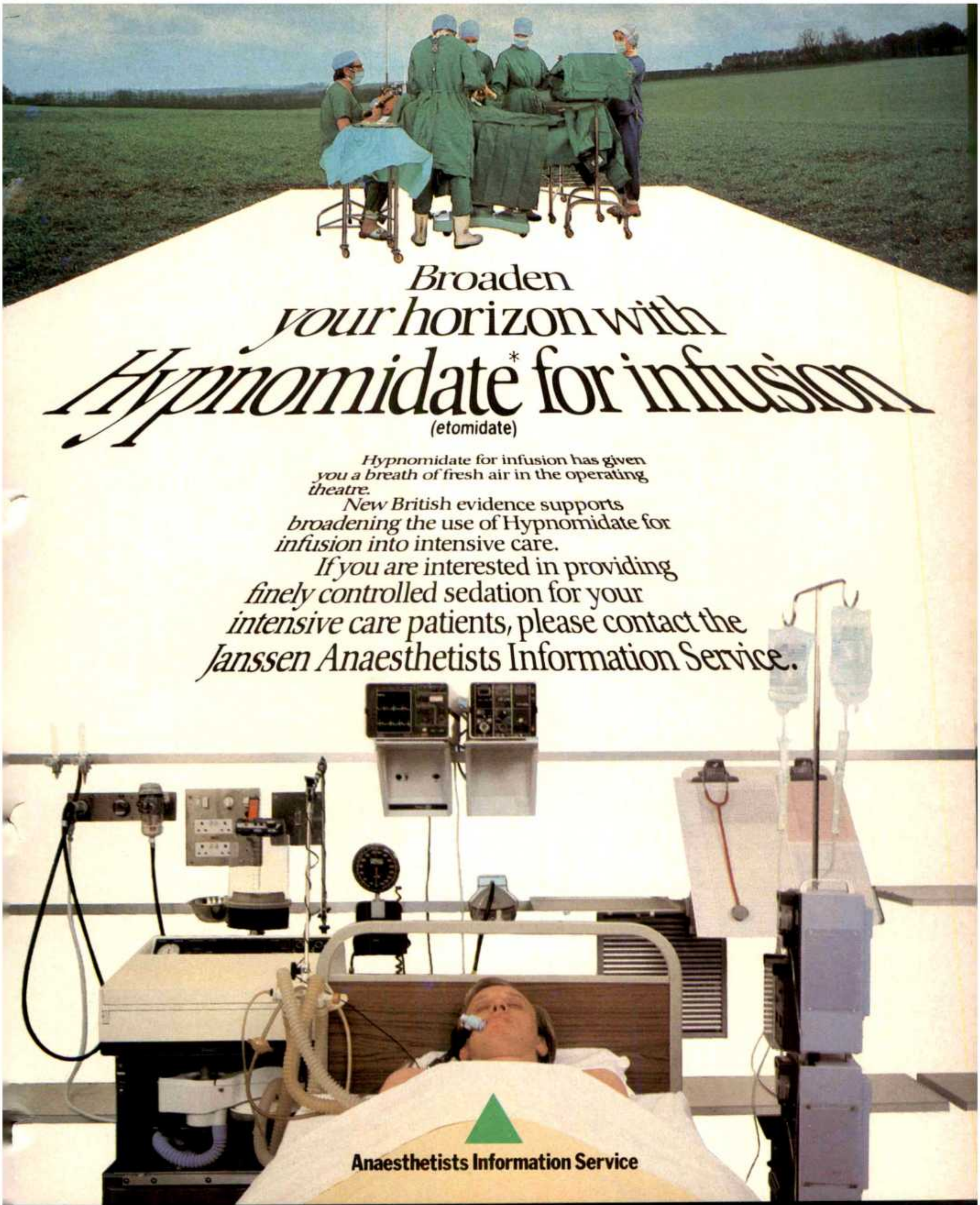
Twenty-five reprints of articles will be dispatched to the authors after publication. Further reprints can be supplied if application is made on the order form attached to the proofs. The order form should be returned with the proofs.



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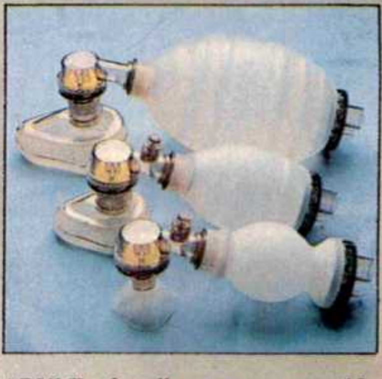

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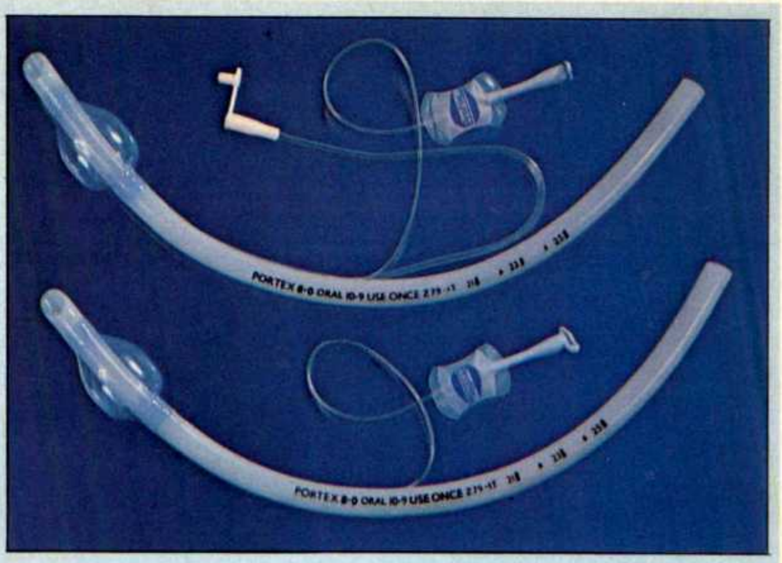

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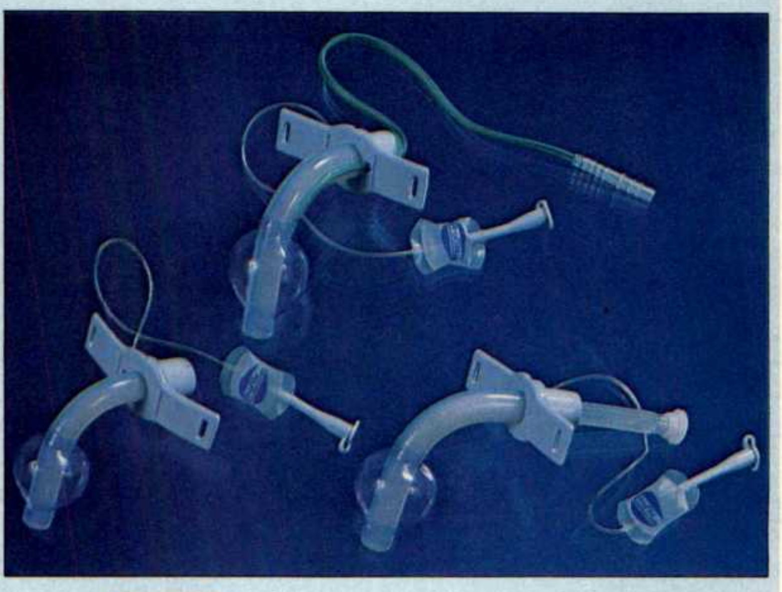

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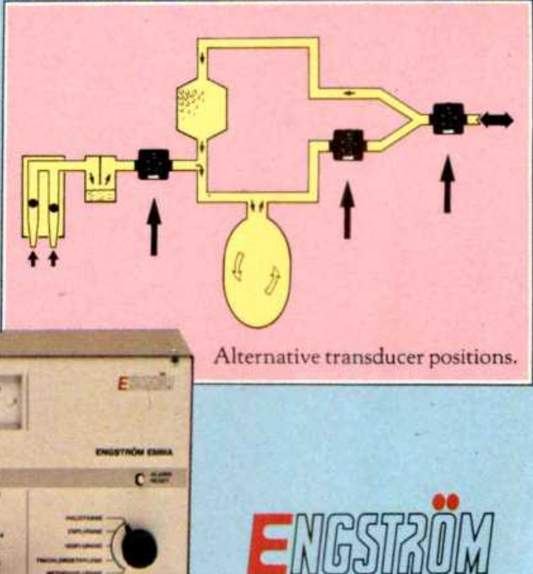

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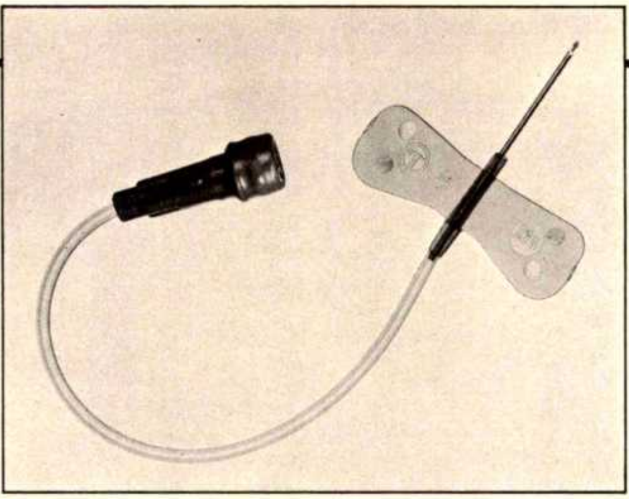

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1. Moore DC 1979 "Regional Anesthesia Techniques" VI P34.

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Information on registration and abstracts from:
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Executive Secretary IASP,
130a Summit Ave., Rm. 101,
Seattle, WA 98101, U.S.A.
(Telephone: 206-292-7521)

---

## BRISTOL ANAESTHETIC CLUB

**Wednesday, November 3, 1982**

A meeting will be held at 8 p.m. at Frenchay Postgraduate Centre, Frenchay Hospital, Bristol.

Speaker: Dr John Nunn—"Surgery in the Egyptian Old Kingdom".

All enquiries to Mrs Judy Seward (Telephone (0272) 565656, ext 251).

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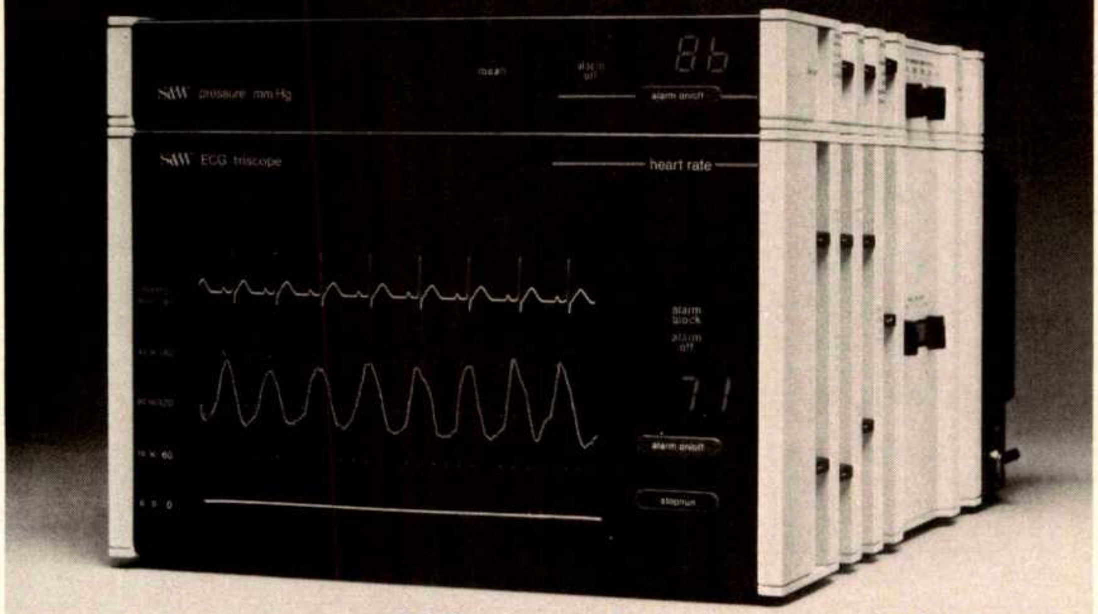

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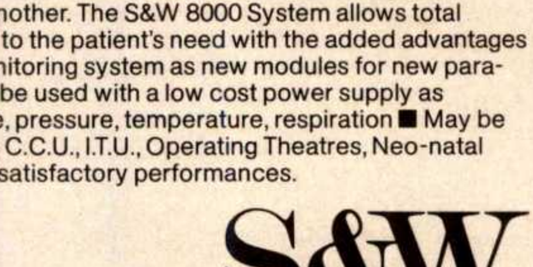

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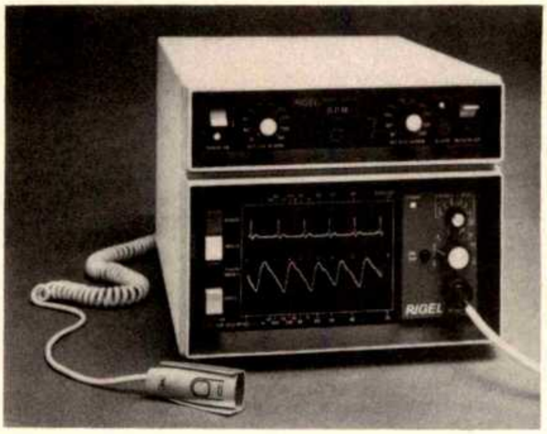

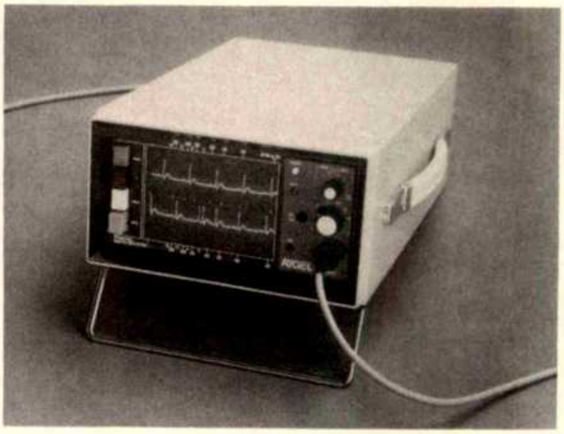

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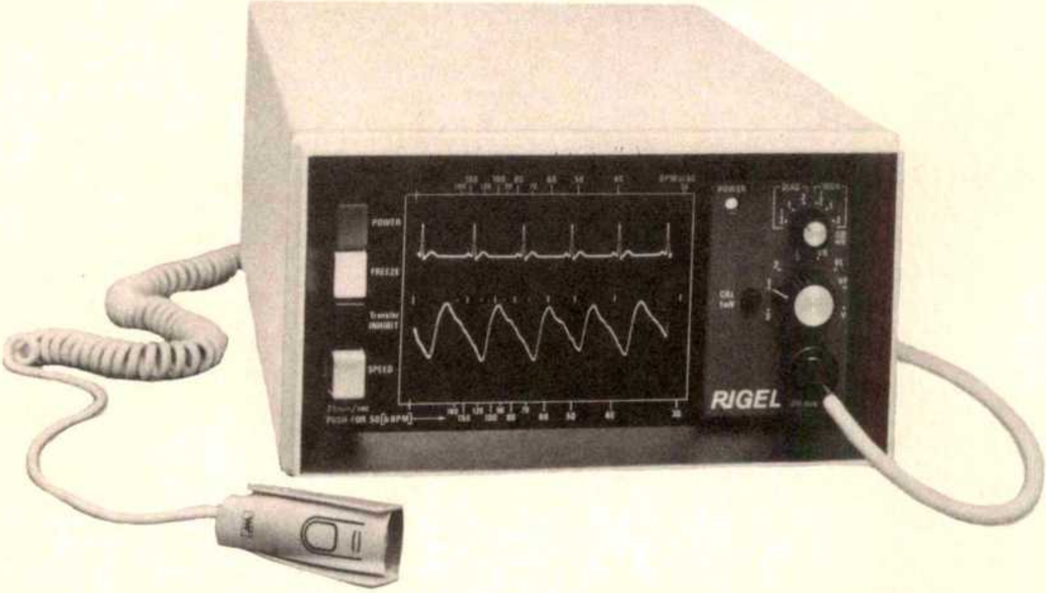

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c/o Dr W. Fitch,
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Tel. 041 552 3535 Extn 5446

Please note that this differs from the address notified in the April issue of the Journal. All business communications to the publishers will continue to be received by: Scientific & Medical Division, The Macmillan Press Ltd, Houndmills, Basingstoke, Hampshire RG21 2XS.

*"I would have everie man write what he knowes and no more."*—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 54, No. 10 OCTOBER 1982

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# EDITORIAL

## ALFENTANIL

There are approximately 15 narcotic analgesics available for clinical use in Britain; all have a similar pattern of therapeutic effect. Morphine remains perhaps the most widely used drug, although fentanyl has found extensive use in anaesthetic practice, primarily because a single dose has a faster onset and shorter duration of action than has morphine.

Alfentanil, developed from fentanyl, continues a pattern of research leading to the production of narcotic analgesics with similar pharmacological actions but differing durations of effect. Alfentanil is the shortest-acting narcotic analgesic available; it has a very rapid onset of action, and about one-third of the duration of effect of fentanyl (Brown, Pleuvry and Kay, 1980). At first sight it would appear to be a very attractive addition to an anaesthetist's pharmacopoea, especially for use where the action of fentanyl is considered to be too prolonged, or when very rapid adjustment of depth of narcosis or degree of analgesia is required.

The introduction of a new drug into clinical practice is, however, never simple. Alfentanil was first used clinically in 1977 (De Castro, personal communication), but extensive clinical use has had to await further assessments of toxicity, a wider appraisal of the clinical effectiveness of the drug and evaluation of suitable techniques for clinical use.

Toxicology studies by the manufacturers are now complete and the results have been presented to the Committee on Safety of Medicines (U.K.), and the Food and Drug Administration (U.S.A.), with a view to obtaining licences for the introduction of alfentanil into clinical practice. Some studies indicate a high degree of safety with alfentanil; the therapeutic index ($LD_{50}/ED_{50}$) in rats is 1080, compared with pethidine 4.7, morphine 71 and fentanyl 277, death being induced by respiratory failure (Niemeegers, 1980). Cardiac and haemodynamic effects in dogs show cardiovascular stability even with very large doses of alfentanil; a negative inotropic effect was only observed after a massive dose of 5 mg kg$^{-1}$ i.v., equivalent to morphine 150 mg kg$^{-1}$ (De Castro et al., 1979). In general, the toxic reactions to alfentanil are similar to those found with other narcotic analgesics, so that no fertility, embryonic or teratogenic effects, and no subacute toxicity have been observed. The effects of alfentanil are permanently reversible by naloxone, which has a longer duration of action than alfentanil (Niemegeers, 1981). In clinical practice one may anticipate respiratory depression, nausea and vomiting and perhaps some peripheral vasodilatation, as with other narcotic analgesics. Euphoria also seems to occur (Kay and Pleuvry, 1980), and with the rapid onset of action of alfentanil it would be surprising if the potential for addiction in humans did not exist, although whether such a short-acting drug would ever attract those addicted to narcotics is debatable.

Pharmacokinetic studies will also form a basis for rational and effective clinical use of alfentanil. In man, after a single i.v. injection, plasma concentrations decrease rapidly, because of redistribution, as with fentanyl. Distribution phase half-life time is short—about 10 min—so that 90% of the administered dose leaves the plasma within 30 min. Elimination phase half-life is also short, about 90 min, compared with that of fentanyl which is about 220 min (Bower and Hull, 1982). Cumulation of alfentanil seems likely to be much less than that seen with fentanyl, indicating that its use in i.v. infusion techniques would not be inappropriate. Alfentanil is metabolized into a large number of inactive metabolites which are excreted through the urine.

Published clinical experiences with alfentanil correlate well with pharmacological studies. There seems to have been three main areas of clinical use. Surprisingly, perhaps, the application first and most widely studied seems to have been the use of very high doses, given by infusion; surely an unusual approach to the initial clinical application of a new drug! After De Castro's early studies of this technique, subsequent use has been mainly in patients undergoing major cardiac surgery where cardiovascular stability has been a feature (Wauquier et al., 1980; de Lange et al., 1981). Doses of alfentanil in excess of 120 $\mu g\,kg^{-1}$ have also been used to induce anaesthesia, reflecting the rapid onset of narcotic action (Spierdijk et al., 1980; de Lange et al., 1981). Induction of anaesthesia took longer with alfentanil than with thiopentone or etomidate, but was faster than when midazolam was used (Nauta et al., 1981).

Alfentanil has also been used in small doses for operations of short duration. In an early study of alfentanil given as a supplement to methohexitone and nitrous oxide anaesthesia, problems arose because of respiratory depression in spontaneously ventilating patients (Kay and Stephenson, 1980), but lack of experience with the drug undoubtedly contributed to the difficulties seen. In subsequent studies in paralysed patients (van Leeuwen and Deen, 1981; Kay and Cohen, 1982) no such problems arose, and the advantage of faster recovery after alfentanil compared with fentanyl was observed. In a further study of i.v. anaesthesia for minor surgery, Althesin with added alfentanil gave better anaesthesia than Althesin alone (Kay, 1981). In women undergoing minor surgery Sinclair and Cooper (1982) also showed faster recovery in patients who received alfentanil than in those who received fentanyl, or no analgesic. It is apparent from the investigations so far reported that alfentanil is useful in a wide variety of clinical situations, and is likely to find extensive use in anaesthetic practice.

There are hazards of alfentanil, however, which may delay its widespread clinical use. The rapid termination of effect of alfentanil can lead to unexpected onset of inadequate analgesia, as well as fast recovery. Furthermore, anaesthesia using alfentanil tends to be less stable than that achieved using other narcotic analgesics, except when administered with an infusion technique. The extent of cumulation, during continuous infusion, has yet to be properly evaluated, and it is likely that we will find that, as with fentanyl, increasing total dosage of alfentanil will risk increasing and persistent degrees of respiratory depression as redistributed drug re-enters the circulation.

The injudicious, or even over-rapid administration of alfentanil, perhaps precipitated by unexpected onset of inadequate anaesthesia, can readily lead to apnoea, especially during nitrous oxide anaesthesia (Andrews et al., 1982). The duration of apnoea induced by a single small dose (0.5 mg) of alfentanil can be several minutes. The drug, whatever the therapeutic index, is only as safe as the anaesthetist giving it, and alfentanil can readily precipitate lethal conditions.

*B. Kay*

## REFERENCES

Andrews, C. J. H., Sinclair, M., Dye, A., Dye, J., Harvey, J., and Prys-Roberts, C. (1982). The additive effects of nitrous oxide on respiratory depression in patients having fentanyl or alfentanil infusions. *Br. J. Anaesth.*, 54, 1129.

Bower, S., and Hull, C. (1982). Comparative pharmacokinetics of fentanyl and alfentanil. *Br. J. Anaesth.*, 54, 871.

Brown, J. H., Pleuvry, P. J., and Kay, B. (1980). Respiratory effects of a new opiate analgesic, R 39209, in the rabbit: a comparison with fentanyl. *Br. J. Anaesth.*, 52, 1101.

De Castro, J., van de Water, A., Wouters, L., Xhonneux, R., Reneman, R., and Kay, B. (1979). Comparative study of cardiovascular, neurological and metabolic side effects of eight narcotics in dogs. Pethidine, piritramide, phenoperidine, fentanyl, R 39209, sufentanil, R 34995. *Acta, Anaesthesiol. Belg.*, 30, pp. 5, 55, 71.

Kay, B. (1981). Alfentanil and Althesin anaesthesia for minor surgery. *Proc. Eur. Acad. Anaesth.* (ed. M. Vickers) Berlin: Springer Verlag. (In press).

——Cohen, A. T. (1982). Clinical experience with alfentanil. *Anaesthesia*, 37, 369.

——Pleuvry, B. J. (1980). Human volunteer studies of alfentanyl. *Anaesthesia*, 35, 952.

——Stephenson, D. K. (1980). Alfentanyl, initial clinical experience with a new narcotic analgesic. *Anaesthesia*, 35, 1197.

de Lange, S., Stanley, T. H., Boscoe, M. J., de Bruijn, N., Philbin, D. M., and Coggins, C. H. (1981). Antidiuretic hormone responses during coronary artery surgery with sufentanil–oxygen and alfentanil–oxygen anesthesia in man. *Anesthesiology*, 55, Suppl. A47.

van Leeuwen, L., and Deen, L. (1981). Alfentanil, a new, potent and very short acting morphinomimetic for minor operative procedures. A pilot study. *Anaesthesist*, 30, 115.

Nauta, J., de Lange, S., Koopman, D., Spierdijk, J., and Stanley, T. H. (1981). Anesthetic induction with alfentanil: comparison with thiopental, midazolam and etomidate. *Anesthesiology*, 55, Suppl. A255.

Niemegeers, C. J. E. (1980). The acute intravenous toxicity of alfentanil (R 39209) in mice and rats. Janssen Pharmacuetica, Preclinical Research Report R 39209/8 October.

——(1981). Complete and irreversible antagonism of the effects of alfentanil by a single dose of naloxone. Janssen Pharmacuetica, Preclinical Research Report R 39209/16, August.

Sinclair, M., and Cooper, G. M. (1982). Assessment of recovery from day-case anaesthesia supplemented with alfentanil. *Br. J. Anaesth.*, **54**, 1138.

Spierdijk, J., Van Kleef, J., Nauta, J., Stanley, T. H., and de Lange, S. (1980). Alfentanil, a new narcotic anesthetic induction agent. *Anesthesiology*, **53**, 532.

Wauquier, A., Van den Broeck, W. A. E., Sebel, P. S., Bovill, J. G., and Rog, P. (1980). Computer analysis of the EEG effects of alfentanil anaesthesia during open heart surgery. Janssen pharmaceutical, Clinical Research Report, R 39209/1, October.

*Br. J. Anaesth.* (1982), 54, 1015

# STATUS OF NEONATES DELIVERED BY ELECTIVE CAESAREAN SECTION

J. S. CRAWFORD AND P. DAVIES

## SUMMARY

A series of 144 elective Caesarean sections is reported. One hundred and five patients had no evidence of placental dysfunction (group A), of whom 57 (40 with vertex presentation) received extradural analgesia. The remaining 39 patients comprised group B. The uterine incision to delivery (U–D) interval was little influenced by presentation, but was longer with extradural block. Among group A patients Apgar-minus-colour scores and the time to sustained respiration after general anaesthesia were poorer than after extradural analgesia, breech presenting infants being prominent in this regard. The contrast was marked when the U–D interval was relatively prolonged. When the U–D interval was less than 90 s the infants born under extradural analgesia were marginally more acidotic than those born under general anaesthesia; in the latter there was a correlation between the duration of the U–D interval and neonatal acidosis, a feature which was not evident in the extradural series. The small numbers of group B cases precluded statistical evaluation, but the results reflected contrasts similar to those found among group A patients.

Several studies have compared the condition of infants delivered by elective Caesarean section under general anaesthesia with that when regional analgesia was provided (Datta and Brown, 1977; James et al., 1977; Palahniuk et al., 1977; Hollmén et al., 1978; Downing, Houlton and Barclay, 1979; Fox et al., 1979). The opinion of the majority was that infants delivered under regional analgesia were in comparatively better condition. Although the possible influence of the duration of the uterine incision–delivery (U–D) interval was referred to by Downing, Houlton and Barclay (1979) and James and colleagues (1977), consideration has apparently not been given to the possibility that the presentation of the infant at the time of the Caesarean section might influence its condition immediately after birth. A comparative analysis considering these two factors is described.

## PATIENTS AND METHODS

### *Patients*

One hundred and forty-four patients underwent elective Caesarean section—that is, they were not in established labour and their membranes were intact. They were classified according to obstetric status and to the presentation of the fetus at the time of operation. Group A patients ($n = 105$) conformed to the definition previously applied (Crawford, 1962), providing no evidence suggestive of placental dysfunction, being of gestational age at least 36 completed weeks, and with an infant of birth weight at least 2.5 kg. The remaining patients were classified as belonging to group B. Two categories of the mode of presentation were recognized: vertex (Group A, 74 and group B, 33) and breech (group A, 31 and group B, 6), although a small number of instances of transverse lie were included in the latter group.

### *Techniques*

All patients received Mist. mag. trisil. BPC 15 ml immediately before leaving the antenatal ward and were provided with a journey-tilt (Crawford, Burton and Davies, 1973) during transport to either an anaesthetic room (for general anaesthesia) or a delivery room (for initiation of an extradural blockade). Each patient received Hartmann's solution i.v.

The choice between general anaesthesia and extradural analgesia was predominantly dependent upon the decision of the mother made after full explanation. Obstetric preference occasionally contributed to the decision, as did the anaesthetist's consideration of certain attributes such as anticipated difficulty at intubation, maternal obesity and, among group B patients, perinatal fragility.

*General anaesthesia.* Our standard technique was used: a 15° lateral tilt on a wedge; a second dose of

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the antacid was given; pre-oxygenation for 4–5 min followed successively by: hyoscine 0.4 mg i.v., the application of cricoid pressure; thiopentone 250–300 mg i.v.; suxamethonium 100 mg i.v.; endotracheal intubation; maintenance of anaesthesia with an inhaled mixture of nitrous oxide 4 litre min$^{-1}$, oxygen 8 litre min$^{-1}$ and trichloroethylene 0.2 vol% administered via a Howell ventilator; and maintenance of neuromuscular blockade with an i.v. infusion of suxamethonium 1 mg ml$^{-1}$. The interval in minutes between the induction of anaesthesia and complete delivery of the infant (I–D interval) was noted.

Fifty-seven group A patients (including 40 with vertex presentation) received general anaesthesia, as did 22 group B patients (all with vertex presentation).

*Extradural analgesia.* The technique used has been described in detail previously (Crawford, 1980). Briefly, it consists of pre-loading the circulation with at least 1 litre of Hartmann's solution, administering the first dose of 0.5% bupivacaine plain 10–15 ml while the patient sits, and injecting incremental doses (5–10 ml) of this solution with the patient in the horizontal lateral position until satisfactory blockade, extending from T6 to S5, has been achieved. Concurrently, a further 1 litre of Hartmann's solution is infused i.v. When satisfactory blockade has been achieved, the patient is transported to the operating theatre, tilted laterally on a wedge. Oxygen approximately 6 litre min$^{-1}$ is supplied via a loosely-fitting face-mask. The smallest volume of bupivacaine administered before delivery was 20 ml, largest was 71 ml, the mean value being 34.5 ml.

Forty-eight group A patients (including 34 with vertex presentation) received extradural analgesia, as did 17 group B patients (of whom 11 had a vertex presentation).

### *Other observations*

The interval between the initial incision into the myometrium and complete delivery of the infant (U–D interval) was measured precisely in seconds. A sample of maternal blood (usually arterial, occasionally venous) was drawn into a heparinized syringe at the time of delivery. A loop of umbilical cord was secured between two pairs of forceps immediately after delivery, and samples of umbilical vein (UV) and umbilical artery (UA) blood promptly drawn from this into heparinized syringes. The acid–base and respiratory gas values of the three specimens of blood were assayed using a Corning 175 automatic pH/blood-gas system situated adjacent to the theatre.

The Apgar-minus-colour scores at 1 and 5 min ($(A - C)_1$ and $(A - C)_5$) were assessed and recorded by a paediatrician, as was the time to sustained respiration (TSR) (min).

Standard statistical methods were used to compare the groups: one-way analyses of variance and Student's *t* test on appropriate contrasts of the group means. Comparisons of frequency data such as the Apgar scores were made using Chi-squared tests or Fisher's exact test when necessary.

## RESULTS

No patient exhibited a decrease in systolic arterial pressure of 20 mm Hg or greater and none was given a vasopressor.

### *(U–D) intervals (group A) (table I)*

Under general anaesthesia the mean U–D interval was slightly shorter when the fetus was presenting as a vertex than when the presentation was by the breech, and under extradural analgesia the opposite was the case. In neither instance, however, was the difference statistically significant. Among cases of breech presentation, the mean U–D interval was very slightly longer under extradural block than under general anaesthesia. Among cases of vertex presentation the mean U–D interval was significantly longer under extradural analgesia than under general anaesthesia ($P < 0.05$). Inclusion of patients in group B in a similar analysis did not alter these relationships.

TABLE I. *Mean values, with standard error (SEM), of U–D intervals in the several categories of patients in group A*

| Anaesthesia (*n*) | Presentation | U–D interval (s) (Mean ± SEM) |
|---|---|---|
| GA (40) | Vertex | 76.5 ± 7.5 |
| GA (17) | Breech | 87.7 ± 11.5 |
| Extradural (34) | Vertex | 102.8 ± 8.1 |
| Extradural (14) | Breech | 89.3 ± 12.7 |

### *Acid–base values (group A)*

The mean values of the acid–base characteristics of maternal arterial (MA) blood at the time of delivery (table II) reveal that there were only slight differ-

TABLE II. *Mean values of maternal arterial pH, $P_{\text{CO}_2}$ and base excess with standard errors, in the four categories of group A patients. The only statistically significant differences are in respect of the pH and $P_{\text{CO}_2}$ among the total G.A.* v. *the total extradural ($P < 0.001$ in each instance)*

| Anaesthesia/ presentation ($n$) | pH (unit) | $P_{\text{CO}_2}$ (kPa) | BE (mmol litre$^{-1}$) |
|---|---|---|---|
| GA/vertex (40) | 7.479<br>(0.006) | 3.80<br>(0.07) | −0.73<br>(0.29) |
| GA/breech (17) | 7.472<br>(0.013) | 3.80<br>(0.13) | −1.18<br>(0.012) |
| Extradural/vertex (34) | 7.446<br>(0.006) | 4.36<br>(0.06) | −0.02<br>(0.32) |
| Extradural/breech (14) | 7.427<br>(0.011) | 4.53<br>(0.18) | −0.36<br>(1.07) |

TABLE III. *Mean values (SEM) of pH, $P_{\text{CO}_2}$ and base excess in umbilical artery (UA) and umbilical vein (UV) blood in the four sets of group A patients*

| | UA | | | UV | | |
|---|---|---|---|---|---|---|
| Anaesthesia/ presentation ($n$) | pH (unit) | $P_{\text{CO}_2}$ (kPa) | BE (mmol litre$^{-1}$) | pH (unit) | $P_{\text{CO}_2}$ (kPa) | BE (mmol litre$^{-1}$) |
| GA/vertex (40) | 7.330<br>(0.005) | 6.58<br>(0.10) | −2.02<br>(0.28) | 7.402<br>(0.005) | 5.19<br>(0.08) | −1.04<br>(0.23) |
| GA/breech (17) | 7.313<br>(0.012) | 6.83<br>(0.20) | −2.42<br>(0.70) | 7.384<br>(0.010) | 5.40<br>(0.12) | −1.59<br>(0.60) |
| Extradural/vertex (34) | 7.322<br>(0.008) | 6.85<br>(0.13) | −1.96<br>(0.33) | 7.379<br>(0.006) | 5.63<br>(0.07) | −1.13<br>(0.30) |
| Extradural/breech (14) | 7.313<br>(0.009) | 7.02<br>(0.17) | −1.99<br>(0.56) | 7.378<br>(0.007) | 5.75<br>(0.12) | −0.92<br>(0.43) |

ences related to the fetal presentation, but that respiratory alkalosis was more marked in those mothers receiving general anaesthesia than in those delivered under extradural block.

The mean values of the UA acid–base variables (table III) show a slight but not significant tendency for the vertex infants to be less acidotic than the breech. Umbilical vein (UV) pH was significantly greater and UV $P_{\text{CO}_2}$ significantly less among the entire GA group when contrasted with the entire extradural analgesia group ($P < 0.05$ for pH and $P < 0.001$ for $P_{\text{CO}_2}$). Correspondingly, there were no significant differences in materno–fetal gradient related to presentation, but the gradients MA–UA and MA–UV were significantly greater for pH and $P_{\text{CO}_2}$ (both $P < 0.02$) in the general anaesthesia series than in the extradural series.

### *Acid–base status and I–D interval (group A)*

The I–D interval among patients with vertex presentation ranged from 10 min to 31 min, and among breech presentations from 10 min to 23 min.

Scatter plots of the acid–base variables against the duration of the I–D interval showed a good deal of apparently random fluctuation in each group and no evidence was found of any worthwhile relationship or correlation.

### *Acid–base status and U–D interval (group A)*

Almost all the scatter plots of acid–base values against U–D interval from the infants delivered under extradural analgesia, whether breech or vertex, showed apparent randomness and absence of correlation. In the general anaesthesia groups, there was more evidence of a tendency for long U–D times to be associated with increasing acidosis, with significant correlations particularly in the larger vertex group. The most notable correlations with U–D interval (all statistically significant at $P < 0.03$) were those with UA pH ($-0.32$); UA $P_{CO_2}$ (0.30); UV pH ($-0.33$) and UV $P_{CO_2}$ (0.37), but even these correlations suggest only a weak relationship.

This contrast between the methods of anaesthesia can be seen by comparing patients in whom the U–D interval did not exceed 90 s with the remainder (table IV). In the extradural series the differences in acid–base status of the neonates were very small and without statistical significance. In the general anaesthesia series, the infants delivered after a U–D interval of more than 90 s were significantly more acidotic than were the remainder.

### *Apgar-minus-colour scores and time to sustained respiration (group A)*

A comparison of the Apgar-minus-colour scores and of TSR less than 1 min can be seen from the distribution of the actual scores. Table V shows the large proportion of very low scores in breech infants delivered under general anaesthesia, and that those infants presenting by the vertex had a higher frequency of low scores in the general anaesthesia group than in the extradural analgesia series. In fact, the general anaesthesia group had a significantly lower percentage of perfect $(A-C)_1$ scores and TSR of less than 1 min than the extradural analgesia group (both $P < 0.05$) for both breech and vertex presentations.

TABLE IV. *Acid–base means (SEM) of umbilical artery (UA) and umbilical vein (UV) blood from patients in group A (elective Caesarean section) classified in respect of the method of anaesthesia and of the duration of the uterine incision – delivery (U–D) interval, with probability levels associated with significance tests for comparing the two U–D groups*

| | General anaesthesia | | | Extradural | | |
|---|---|---|---|---|---|---|
| | U–D<90 ($n=42$) | U–D>90 ($n=15$) | $P$ | U–D<90 ($n=26$) | U–D>90 ($n=22$) | $P$ |
| UA pH (unit) | 7.334<br>(0.004) | 7.301<br>(0.031) | <0.005 | 7.318<br>(0.008) | 7.320<br>(0.010) | n.s. |
| UA $P_{CO_2}$ (kPa) | 6.52<br>(0.09) | 7.04<br>(0.24) | <0.02 | 6.86<br>(0.12) | 6.94<br>(0.18) | n.s. |
| UA BE (mmol litre$^{-1}$) | −1.95<br>(0.32) | −2.67<br>(0.56) | n.s. | −2.14<br>(0.45) | −1.76<br>(0.33) | n.s. |
| UV pH (unit) | 7.402<br>(0.005) | 7.382<br>(0.010) | <0.05 | 7.379<br>(0.006) | 7.378<br>(0.008) | n.s. |
| UV $P_{CO_2}$ (kPa) | 5.14<br>(0.06) | 5.57<br>(0.17) | <0.01 | 5.73<br>(0.08) | 5.59<br>(0.09) | n.s. |
| UV BE (mmol litre$^{-1}$) | −1.16<br>(0.29) | −1.13<br>(0.43) | n.s. | −0.83<br>(0.36) | −1.34<br>(0.32) | n.s. |

TABLE V. *Apgar-minus-colour scores at 1 min ($(A-C)_1$) and at 5 min ($(A-C)_5$), and number of instances of time-to-sustained respiration (TSR) of at least 1 min, in group A patients*

| | $(A-C)_1$ | | | | $(A-C)_5$ | | | | TSR |
|---|---|---|---|---|---|---|---|---|---|
| | 0–3 | 4–6 | 7 | 8 | 0–3 | 4–6 | 7 | 8 | >1 min |
| GA/vertex (40) | 2 | 4 | 3 | 31 | 1 | 2 | 1 | 36 | 7 |
| GA/breech (17) | 2 | 5 | 0 | 10 | 0 | 4 | 2 | 11 | 7 |
| Extradural/vertex (34) | 0 | 0 | 2 | 32 | 0 | 0 | 0 | 34 | 0 |
| Extradural/breech (14) | 0 | 1 | 0 | 13 | 0 | 0 | 0 | 14 | 0 |

### *(A − C) scores and TSR in relationship to I–D and U–D intervals*

In view of the previous results, it is notable that the series of breech presentations delivered under general anaesthesia, which was the group with the worst occurrence of imperfect scores and prolonged TSR, did not have the greatest mean U–D value, as might have been expected. The general pattern of results concerning the relationship of the two intervals to the $(A - C)_1$ scores can be seen from figures 1 and 2.

Among vertex presentations delivered under general anaesthesia, the clinical condition of the infant at delivery (the 1-min score) was apparently not influenced by the duration of the I–D interval, and the same held true, at least up to 19 min, for breech presentations. However, long durations of the U–D interval appeared to be associated with poor 1-min scores in infants delivered under general anaesthesia, whether they presented by the vertex or breech, but to be of little or no significance to the clinical status of infants delivered under extradural block, which was rarely imperfect.

### *Pre-eclampsia and diabetes*

There was only one breech presentation (a diabetic delivered under extradural analgesia) in these two categories. Among the 19 infants presenting by the vertex, 13 were delivered under general anaesthesia (including seven diabetics) and six under extradural block (four diabetic). The sample sizes are too small to make statistical tests meaningful. However, the mean values of acid–base status revealed that these infants were more acidotic than were those in group A, and the (A − C) scores of those infants delivered under general anaesthesia were considerably poorer than those of group A infants, although the six group B infants delivered under extradural block exhibited almost perfect (A − C) scores.

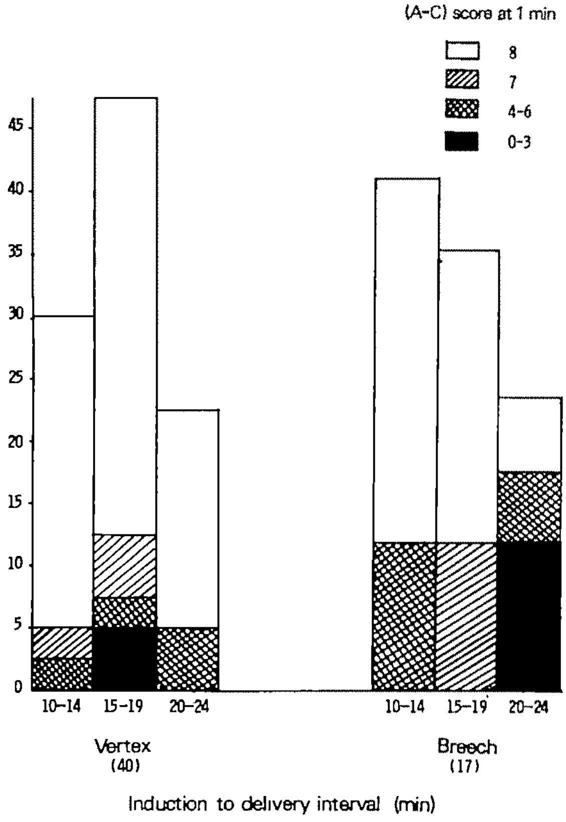

FIG. 1. Distribution of group A patients grouped according to duration of induction–delivery interval, showing proportional distribution of 1-min Apgar-minus-colour scores in each set.

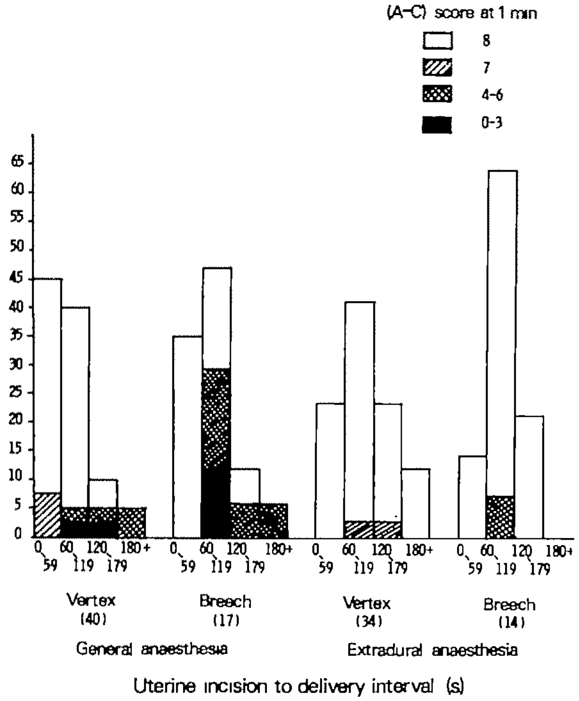

FIG. 2. Distribution of group A patients grouped according to duration of uterine incision to delivery interval, showing proportional distribution of 1-min Apgar-minus-colour scores in each set.

## DISCUSSION

The results of this study confirmed our earlier finding (Crawford, Burton and Davies, 1973) that, in the context of our obstetric practice, neither the acid–base status nor the (A−C) scores of group A infants delivered under general anaesthesia was systematically influenced by the duration of the I–D interval. A recent report by Datta, Ostheimer and colleagues (1981) suggested that the extent of the I–D interval was of significant import to the condition of the infant. However, in their series a large number of infants (39 of a total 60) were delivered less than 8 min after induction, whereas in our series none was delivered in less than 10 min. We suggest, therefore, that if protraction of the I–D interval does adversely affect the infant, the tendency is not consistently progressive after the first 10 min.

The presentation of the infant by breech or vertex did not appear consistently to influence the duration of the U–D interval, suggesting that a breech presentation, in our service, does not impose great difficulty in extracting the infant from within the uterine cavity. The U–D interval tended to be longer when the operation was conducted under the extradural analgesia. This perhaps reflects pressure upon the obstetrician to act with more deliberation and gentleness when the patient is awake, and might have been expected to lead to increase in the frequency of fetal acidosis, in view of our previous observation (Crawford and Davies, 1975). Indeed, Downing, Houlton and Barclay (1979) observed such to be the case in their series, and James and co-workers (1977) presented evidence suggestive of a similar relationship. However, whilst our former contention holds true in repect to general anaesthesia, we have found no evidence of it here for Caesarean sections conducted under extradural block. Datta, Ostheimer and colleagues (1981) reported a similar distinction between general anaesthesia and spinal analgesia and suggested that the contrast reflected the effects upon the fetus of a more prolonged period of maternal hyperventilation under general anaesthesia. This explanation could be considered as reasonable in the context of their study, because, as has been mentioned, their I–D interval was often less than 8 min and, apparently, their U–D interval was greater than 3 min in 29 of 115 patients (whereas we encountered a U–D interval greater than 3 min in only three out of 57 patients). It is difficult to see how such a suggestion could apply to our series, such that 90–180 s of "hyperventilation" superimposed upon a preceding period of 10–31 min of similar ventilatory management was sufficient to cause the distinction depicted in table VI. Furthermore, bearing in mind that in pregnancy the normal $P\text{CO}_2$ of MA blood is approximately 4.5 kPa, it is apparent that our patients were not strikingly hypocarbic.

It could be argued that patients who received general anaesthesia had a relatively high level of circulating catecholamines, causing a reduction in placental blood flow and thus leading to increased fetal acidosis, whereas this response to surgery was blocked by regional analgesia. However, none of the patients reported awareness or unpleasant dreams during the operation. Also, if the distinction between general anaesthesia and extradural analgesia were related to catecholamine response we would anticipate finding a correlation between the fetal acid–base status and the I–D interval. It is, however, possible that a regional block prevents a local vasoconstrictor response which, under general anaesthesia, is evoked by handling of the uterus. We must confess to having no convincing explanation of the observed contrast between general anaesthesia and extradural analgesia in respect of the differing effects of prolongation of the U–D interval upon the acid–base status of the neonate.

We confirmed our previous findings (Crawford, Burton and Davies, 1973; Crawford and Davies, 1975) about the clinical condition ((A−C) scores) of the neonates. The duration of the I–D interval had little effect in determining the clinical condition of the infant at delivery, but a long U–D interval was associated with poor condition. Previously, we postulated that this could be a result either of interference with utero–placental blood flow during the time elapsing between incision of the myometrium and complete delivery of the infant, or of prolonged handling of the infant whilst it was being extracted from within the uterine cavity. However, it does not appear (fig. 2) that the duration of the U–D interval substantially affects the condition of the infant delivered under extradural analgesia. These findings complement those reported by Datta, Ostheimer and colleagues (1981) and, as suggested above, might reflect the fact that an extradural block inhibits a local vasoconstrictor response to handling of the uterus.

A further contrast is that between vertex and breech presentations delivered under general anaesthesia. The clinical condition at delivery of such infants presenting by the breech was deplorably poor. This partly reflects the slightly longer U–D interval associated with breech infants (fig. 2), but this is unlikely to be the complete explanation. Since the head of the breech infant is the last part to be delivered, and the infant is being stimulated during delivery, it will tend to gasp and inhale liquor, thus inducing reflex apnoea. However, a similar contrast between vertex and breech was not seen among infants delivered under an extradural block, the vast majority of whom had perfect scores. It would be logical to suppose that when infants were mildly depressed—as by transplacentally derived anaesthetic drugs—they would be less likely to gasp during delivery and that hence the "extradural breech" infants would exhibit a greater tendency to depression. However, the groups under review are small and confirmation of our observation is needed before seeking further explanation.

These findings have some relevance to clinical practice. Although a Caesarean section conducted under extradural analgesia tends to be associated with a comparatively long U–D interval, prolongation of this interval beyond 90 s—at least up to 3 min—is not associated with the increase in neonatal acidosis observed among Caesarean sections conducted under general anaesthesia. Among infants delivered following a U–D interval of less than 90 s, those whose mothers have a general anaesthetic tend to be slightly less acidotic than those delivered under extradural block, but this contrast is reflective mainly of the maternal hypocarbia associated with our techniques of general anaesthesia.

The clinical condition of the infants provides a much more distinct contrast. Infants delivered under extradural analgesia are in better condition than those delivered under general anaethesia, and this is particularly so for infants presenting by the breech. Furthermore, when delivery is conducted under general anaesthesia, infants presenting by the breech tend to be considerably more depressed than do vertex-presenting infants. The latter finding is of relevance in the definition of procedures for pertinent clinical investigations:

(i) if techniques of general anaesthesia for elective Caesarean section are to be compared, the matching of cases must include reference to the presentation of the infant;

(ii) when attempts are made to assess the respective merits of vaginal delivery of a breech and of abdominal delivery, the latter group should include only those cases in which the infant was presenting by the breech at the time of operation.

The question might be raised whether the fact that the infants delivered under general anaesthesia, and especially those presenting by the breech, exhibited a notably high frequency of clinical depression is of any serious import, in view of the fact that their acid–base status was as good as that of the infants delivered under extradural block. There are two answers: first, it is preferable to avoid, if possible, depression of an infant at the time of delivery; second, in certain categories, such as immaturity or infants who have been subjected to asphyxia within the uterus, clinical depression as a result of the choice of general anaesthesia rather than extradural analgesia could be of considerable significance to the post-natal course.

A related point is that when a Caesarean section is performed for the delivery of a pre-term infant there is likely to be difficulty in extracting the infant through the incision made in a poorly-formed lower uterine segment and, as a result, a relatively prolonged U–D interval. Our results suggest that, if such an operation is performed under general anaesthesia, the immature infant will, as a result of the prolonged U–D interval, show more signs of clinical depression than would have been the case had an extradural block been provided.

The cord (and maternal) blood acid–base values derived from our few diabetic patients delivered under extradural analgesia matched quite closely those reported by Datta, Brown and colleagues (1981) from a series in which maternal hypotension was not a feature. The difficulties inherent in classifying the extent of placental dysfunction in patients with either diabetes or moderate or severe pre-eclampsia render it almost impossible to make a valid comparison of techniques of anaesthesia for such patients. However, we did observe that the Apgar scores of infants in these categories were better in the extradural analgesia series than in the group of patients who received general anaesthesia.

## REFERENCES

Crawford, J. S. (1962). Anaesthesia for section: a proposal for evaluation with analysis of a method. *Br. J. Anaesth.*, **34**, 179.

—— (1980). Experiences with lumbar extradural analgesia for Caesarean section. *Br. J. Anaesth.*, **52**, 821.

—— Burton, M., and Davies, P. (1973). Anaesthesia for section: further refinements of a technique. *Br. J. Anaesth.*, 45, 726.

—— Davies, P. (1975). A return to trichloroethylene for obstetric anaesthesia. *Br. J. Anaesth.*, 47, 482.

Datta, S., and Brown, W. U. (1977). Acid–base in diabetic mothers and their infants following general or spinal anesthesia for Cesarean section. *Anesthesiology*, **47**, 272.

Datta, S., Brown, W. U., Ostheimer, G. W., Weiss, J. B., and Alper, M. H. (1981). Epidural anesthesia for Cesarean section in diabetic parturients: maternal and neonatal acid–base status and bupivacaine concentration. *Anesth. Analg. (Cleve.)*, 60, 574.

—— Ostheimer, G. W., Weiss, J. B., Brown, W. U., and Alper, M. H. (1981). Neonatal effect of prolonged anesthetic induction for Cesarean section. *Obstet. Gynecol.*, 58, 331.

Downing, J. W., Houlton, P. C., and Barclay, A. (1979). Extradural analgesia for Caesarean section: a comparison with general anaesthesia. *Br. J. Anaesth.*, 51, 367.

Fox, G. S., Smith, J. B., Namba, Y., and Johnson, R. C. (1979). Anesthesia for Cesarean section: further studies. *Am. J. Obstet. Gynecol.*, 133, 15.

Hollmén, A. I., Jouppila, R., Koivisto, M., Maatta, L., Pilhajaniemi, R., Puukka, M., and Rantakyla, P. (1978). Neurologic activity of infants following anesthesia for Cesarean section. *Anesthesiology*, 48, 350.

James, F. M., Crawford, J. S., Hopkinson, R., Davies, P., and Naiem, H. (1977). Comparison of general anesthesia and lumbar epidural analgesia for elective Cesarean section. *Anesth. Analg. (Cleve.)*, 56, 228.

Palahniuk, R. J., Scatliff, J., Biehl, D., Wiebe, H., and Sankaran, K. (1977). Maternal and neonatal effects of methoxyflurane, nitrous oxide and lumbar epidural anaesthesia for Caesarean section. *Can. Anaesth. Soc. J.*, 24, 586.

## ETAT DES NOUVEAUX-NES ACCOUCHES PAR CESARIENNE REGLEE

### RESUME

L'étude porte sur une série de 144 césariennes règlées. Cent cinq patientes n'avaient pas de signes de dysfonctionnement placentaire (groupe A) et parmi celles-ci 57 (dont 40 présentations du vertex) ont reçu une analgésie péridurale. Les 39 autres patientes constituaient le groupe B. Le délai entre l'incision et l'extraction (I–E) était peu influencé par la présentation mais plus long en cas de bloc péridural. Parmi les patientes du groupe A, les scores d'Apgar-sans-la-coloration et le temps d'installation d'une ventilation soutenue étaient plus mauvais après anesthésie générale qu'après analgésie péridurale, ceci étant particulièrement marqué dans les présentations du siège. Le contraste était marqué quand l'intervalle I–E était relativement prolongé. Lorsque l'intervalle I–E était inférieur à 90 s, les enfants nés sous analgésie péridurale étaient plutôt plus en acidose que ceux nés sous anesthésie générale; parmi ces derniers il y avait une corrélation entre la durée de l'intervalle I–E et l'acidose néonatale, ce qui n'était pas évident dans la série d'analgésies péridurales. Le petit nombre de sujets du groupe B empêchait une analyse statistique mais les résultats reflétaient des contrastes semblables à ceux observés chez les sujets du groupe A.

## DER ZUSTAND VON NEUGEBORENEN, DIE DURCH ELEKTIVEN KAISERSCHNITT ZUR WELT GEKOMMEN SIND

### ZUSAMMENFASSUNG

Es wird über eine Reihe von 144 elektiven Kaiserschnitten berichtet. Von einhundertfünf Patienten ohne Anzeichen einer Dysfunktion der Plazenta (Gruppe A), erhielten 57 (40 mit Scheitellage) eine Periduralanästhesie. Der Zeitabstand zwischen Uterusinzision und Geburt (U–D) wurde durch die Lage wenig beeinflusst, war aber länger beim Periduralblock. Unter den Patienten in Gruppe A war der Apgar-Index und die Zeit, die verstrich, bis das Kind atmete, schlechter als nach Periduralanalgesie, besonders bei Kindern mit Beckenlage. Der Unterschied war ausgeprägt, wenn das U–D Intervall relativ verlängert war. Betrug das I–D Intervall weniger als 90 s, dann waren die Kinder, die unter Periduralanästhesie geboren wurden, stärker azidotisch als die unter Allgemeinnarkose Geborenen. Bei den letzteren gab es eine Korrelation zwischen der Dauer des I–D Intervalls und der Azidose des Neugeborenen, ein Merkmal, das bei der Peridural-Serie nicht auftrat. Die kleine Anzahl von Gruppe B-Fällen schloß eine statistische Auswertung aus, aber die Ergebnisse wiesen auf ähnliche Unterschiede hin, wie sie bei den Patienten von Gruppe-A gefunden wurden.

## ESTADO DE LOS NEONATOS PARTEADOS POR OPERACIÓN CESAREA ELECTIVA

### SUMARIO

Se informa respecto de una serie de 144 operaciones cesáreas electivas. En ciento y cinco pacientes, de los cuales 57 recibieron una analgesia extradural (40 con presentación del vértice), no hubo prueba de disfunción del placenta (Grupo A). Los demás 39 pacientes formaban el Grupo B. El intervalo entre la incisión uterina y el parto (U–D) poco fue influenciado por la presentación pero sí fue más largo con el bloqueo extradural. En los pacientes del Grupo A, las marcas de color-negativo-Apgar y el tiempo de respiración sostenida después de la anestesia general fueron más bajos que después de la analgesia extradural, habiendo una predominancia al respecto con los neonatos de presentación tresera. El contraste fue marcado cuando se prolongó bastante el intervalo U–D. Cuando el intervalo era menos de 90 s., los neonatos nacidos bajo analgesia extradural demostraban una tendencia acidótica marginal mayor de la de los nacidos bajo anestesia general; en estos últimos, existía una correlación entre la duración del intervalo U–D y la acidosis neonatal, un rasgo que no fue evidente en la serie extradural. Las bajas cifras del Grupo B imposibilitaron una evaluación estadística, pero los resultados reflejaban contrastes similares a los encontrados en los pacientes del Grupo A.

*Br. J. Anaesth.* (1982), 54, 1023

# INVESTIGATION OF THE RELATIONSHIP BETWEEN HEAT LOSS AND NITROGEN EXCRETION IN ELDERLY PATIENTS UNDERGOING MAJOR ABDOMINAL SURGERY UNDER GENERAL ANAESTHETIC

F. CARLI, M. M. CLARK AND J. W. WOOLLEN

## SUMMARY

An attempt was made to reduce heat loss in elderly patients undergoing major abdominal surgery. Two groups were studied. In one group, efforts were made to minimize heat loss by using a hot-water humidifier in the anaesthetic circuit, a hot-water circulating mattress under the patient and warming all i.v. fluids. Otherwise, the surgical and anaesthetic techniques were comparable. The same anaesthetic technique of nitrous oxide, oxygen, pancuronium and fentanyl with intermittent positive pressure ventilation was used in all cases. Nitrogen loss was measured in urine collected over 48 h from an indwelling urinary catheter inserted soon after induction of anaesthesia. Prevention of heat loss during anaesthesia and postoperative recovery caused a significant reduction in nitrogen loss.

Human body temperature is maintained within normal limits as a result of the balance between heat production and heat loss. During anaesthesia and surgery, there is a decrease in body temperature caused by impaired heat production and loss of heat by radiation and convection. Anaesthetic agents contribute to heat dissipation by causing cutaneous vasodilatation whilst neuromuscular blocking agents prevent shivering, thus reducing heat production. Inhalation of dry gases and administration of i.v. fluids at room temperature contribute to a decrease in body temperature (Boyan and Howland, 1961). The type of surgery also influences heat loss; thus operations on body cavities cause considerable heat loss (Dyde and Lunn, 1970). Age is an important factor in temperature balance, and the elderly have decreased heat production as well as altered thermoregulatory response (Editorial, 1977).

Ambient temperatures in the operating and recovery rooms used in this study were kept in the range 20–22 °C with a low relative humidity. This is comfortable for staff, but may be detrimental to elderly patients undergoing long operations (Morris, 1971).

Nitrogen excretion was measured in an attempt to quantify the clinical impression that patients were improved by heat conservation. Cuthbertson and Tilstone (1969) and Cuthbertson (1976) showed that, in animals and humans, transfer to a warm environment reduces the nitrogen loss usually seen during the "flow" period following trauma. In these studies, there was a time lag between injury and attempts to maintain normothermia. Benzinger (1969) showed that reduced body temperatures provide a stimulus for increases in basal metabolic rate. During the recovery phase of anaesthesia, any heat debit incurred during operation is repayed by shivering, vasoconstriction and piloerection, which are efficient mechanisms of heat production in the adult at a skin temperature of 33 °C and a core temperature of less than 37 °C. However, oxygen consumption in patients who shiver is increased by 100–400% over basal values (Burton and Edholm, 1955; Roe et al., 1966). In frail, elderly patients already depressed by anaesthetic agents this could lead to arterial hypoxaemia (Bay, Nunn and Prys-Roberts, 1968).

## PATIENTS AND METHODS

Patients aged 60 yr and older were studied; all were classified as ASA II or III. Any patient with a metabolic disorder or who had a significant degree of weight loss or was in a poor nutritional state was excluded since patients who were protein-depleted before operation would be unable to excrete much nitrogen after operation. Patients were randomly

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TABLE I. *Details of patients*

| | *n* | M | F | Age (yr) (SD) | Weight (kg) (SD) | Type of operation | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Stomach | Biliary tract | Bowel |
| Control group A | 9 | 6 | 3 | 70 (9.6) | 67 (13.4) | 4 | 2 | 3 |
| Test group B (attempts to conserve heat) | 11 | 2 | 9 | 76 (5.3) | 58 (12 ) | — | 4 | 7 |

allocated to two groups, A and B (table I). All patients underwent elective major abdominal surgery. Group A served as a control while in group B (afterwards referred to as the test group), efforts were made to minimize heat loss. After premedication with pethidine 1 mg kg$^{-1}$ and phenergan 0.4 mg kg$^{-1}$ i.m. anaesthesia was induced with thiopentone 5 mg kg$^{-1}$. Suxamethonium chloride 1 mg kg$^{-1}$ was used to facilitate intubation and pancuronium bromide 0.1 mg kg$^{-1}$ to provide subsequent relaxation. Maintenance of anaesthesia was with 66% nitrous oxide in oxygen, supplemented by droperidol 0.25 mg kg$^{-1}$ and fentanyl in increments of 50 $\mu$g as indicated clinically. The lungs were ventilated with a minute volume of 100 ml kg$^{-1}$. In the test group, inspired gases were warmed and humidified using a hot-water humidifier (East) set at 50 °C. Fluids were infused i.v. at 4 ml kg$^{-1}$h$^{-1}$ and five patients in each group required blood transfusion during surgery. Those in the test group had all their i.v. fluids warmed at 37 °C using a Grant BN2 blood warming bath.

A Sheffield water circulating mattress was set at a thermostatically controlled temperature of 37 °C and placed under each patient in the test group during surgery. As soon as the operations were completed, a metallized plastic sheet was placed over the patients in the test group to minimize heat loss. Either 0.5% chlorhexidine in spirit or betadine was used to prepare the skin and double drapes were placed over the patient.

The ambient temperature around the patient and the mean skin and core temperatures were monitored before induction, every 30 min during surgery and in the recovery room for 1 h. An electrical thermometer (Comark) was used which had been previously calibrated and checked against a mercury thermometer. Mean skin temperatures were calculated using the four points formula proposed by Ramanathan (1964):

$$T^\circ_{\text{skin}} = 0.3\,(T^\circ_{\text{chest}} + T^\circ_{\text{arm}}) + 0.2\,(T^\circ_{\text{thigh}} + T^\circ_{\text{calf}})$$

Four skin probes were situated lateral to the nipple, on the lateral aspect of the upper arm, the ventral surface of the mid thigh and the lateral aspect of the mid calf. Core temperature was measured by inserting a probe into the auditory canal. Total body temperature was derived from the following equation (Colin et al., 1971):

$$T^\circ_{\text{body}} = 0.66 \times \text{aural canal } T^\circ + 0.34 \times \text{mean skin temperature}$$

$$\text{Total body heat (kJ m}^{-2}) = \frac{T^\circ_{\text{body}} \times 0.83 \times \text{body weight} \times 4.1868}{\text{surface area}}$$

Skin surface area was calculated from the patients' weight and height (Dubois and Dubois, 1915). Heat content related to body surface area could then be derived as could the change in heat content during operation (table II):

TABLE II. *Patient data and temperature changes during operation. Statistically significant difference between values for test and control group:* *P = *0.001*

| | Control group (A) 9 patients | | Test group (B) 11 patients | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| Age (yr) | 70.8 | 9.6 | 76.8 | 5.3 |
| Weight (kg) | 67.1 | 13.4 | 58.4 | 12.1 |
| Surface area (m$^2$) | 1.67 | 0.19 | 1.52 | 0.17 |
| Duration of op. (min) | 145.00 | 23.7 | 155.0 | 44.1 |
| Ambient temperature (°C) | 21.2 | 0.62 | 21.6 | 0.70 |
| Change in body temperature (°C) | −1.03* | 0.35 | −0.16* | 0.26 |
| Change in patient's heat content kJ m$^{-2}$ h$^{-1}$ | −60.7* | 25.1 | −6.8* | 9.1 |
| Body temperature at end of op. (°C) | 35.13* | 0.65 | 35.96* | 0.28 |

$$\mathrm{kJ\,m^{-2}\,h^{-1}} = \Delta \; \frac{T^{\circ}_{\mathrm{body}} \times 0.83 \times \text{body weight} \times 4.1868 \times 60}{\text{surface area} \times \text{duration of operation (min)}}$$

Urine was collected for 48 h from an indwelling bladder catheter inserted at the beginning of the operation. All collecting vessels contained 10 ml of 2% boric acid as preservative. Postoperative fluids were administered according to the procedure: 40 ml $\mathrm{kg^{-1}\,24\,h^{-1}}$, $Na^+$ intake of 3 mmol $\mathrm{kg^{-1}\,24\,h^{-1}}$ and $K^+$ 0.3 mmol $\mathrm{kg^{-1}\,24\,h^{-1}}$. Urinary urea, sodium and potassium concentrations were measured (Technicon SMA 6/60 analyser) over the first and second 24-h periods from the start of the operation. Plasma concentrations were also measured before and after operation. Nitrogen excretion was calculated from the urinary excretion according to the formula:

$$\text{urinary nitrogen} = \text{urinary urea} \; \frac{(\mathrm{mmol\,24\,h^{-1}})}{1000} \times 28 \times \frac{5}{4}\,\mathrm{g\,24\,h^{-1}}$$

assuming that 80% of the waste nitrogen was excreted as urea (Allison, 1974). The catabolic index was calculated according to Bistrian (1979):

$$\text{urinary nitrogen } (\mathrm{g\,24\,h^{-1}}) - (0.5 \times \text{dietary nitrogen } \mathrm{g\,24\,h^{-1}} + 3)$$

Plasma and urinary creatinine concentrations were also measured (Technicon SMA 6/60 analyser). In two patients from the control and three from the test group, the derived "maximal" (or true) urea clearance (Smith, 1951) was corrected to a body surface area of 1.73 $m^2$; the derived creatinine clearances were similarly corrected for body surface area. Statistical analysis of the data was performed using Student's *t* test. Results are presented as mean(± SD) and a statistically significant change was considered to have occurred when *P* values were 0.01 or less.

## RESULTS

The body temperature changes in the two groups during operation are shown in table II. In all patients, normothermia was achieved and maintained within a few hours of recovery.

There was significantly less heat loss in the test group (6.8 kJ $\mathrm{m^{-2}\,h^{-1}}$) compared with the control group (60.7 kJ $\mathrm{m^{-2}\,h^{-1}}$).

These differences were associated with significantly reduced mean postoperative urea excretion in the test group which was less than half that in the control group (table III). The derived nitrogen ex-

TABLE III. *Urinary excretion of urea, nitrogen, sodium and potassium in 24-h period starting from induction of anaesthesia and a further 24-h period following operation. Statistically significant differences between values for test and control groups:* *P < *0.001: statistically significant difference between values for operative and postoperative periods in the same group:* †P = *0.001–0.005;* ‡P = *0.005–0.01*

| | Control group (A) | | | | | | Test group (B) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day of op. | | | After op. | | | Day of op. | | | After op. | | |
| | No. | Mean | SD | No. | Mean | SD | No. | Mean | SD | No. | Mean | SD |
| Urine volume ($\mathrm{ml\,24\,h^{-1}}$) | 8 | 921 | 572 | 9 | 1897 | 832 | 10 | 883 | 587 | 11 | 1435 | 928 |
| Urinary urea ($\mathrm{mmol\,24\,h^{-1}}$) | 8 | 215† | 118 | 9 | 440†* | 157 | 10 | 147 | 79 | 11 | 145* | 67 |
| Urinary nitrogen ($\mathrm{g\,kg^{-1}\,24\,h^{-1}}$) | 8 | 0.12† | 0.06 | 9 | 0.23†* | 0.07 | 10 | 0.09 | 0.06 | 11 | 0.09* | 0.05 |
| Catabolic index | 8 | 4.51‡ | 3.88 | 9 | 12.09‡* | 5.26 | 10 | 2.13 | 2.64 | 11 | 2.35* | 2.31 |
| Serum urea ($\mathrm{mmol\,litre^{-1}}$) | | | | 7 | 6.05 | 1.98 | | | | 10 | 5.13 | 1.38 |
| Urea clearance ($\mathrm{ml\,min^{-1}/1.73\,m^{-2}}$) | | | | 7 | 57.1* | 15.7 | | | | 10 | 23.4* | 10.8 |
| Urinary sodium ($\mathrm{mmol\,24\,h^{-1}}$) | 8 | 47.9 | 49.4 | 9 | 56.0 | 56.8 | 10 | 40.1 | 47.4 | 11 | 46.8 | 44.1 |
| Urinary potassium ($\mathrm{mmol\,24\,h^{-1}}$) | 8 | 63.6 | 31.0 | 9 | 62.4 | 28.7 | 10 | 37.6 | 21.2 | 11 | 27.5* | 14.5 |

TABLE IV. *Urea and creatinine clearance (values in five patients)*

| Patient | | Urea clearance ($ml\ min^{-1}/1.73\ m^{-2}$) | Creatinine clearance ($ml\ min^{-1}/1.73\ m^{-2}$) |
|---|---|---|---|
| 1 | Test group (B) | 20 | 53 |
| 2 | Test group (B) | 22 | 52 |
| 3 | Test group (B) | 6 | 8 |
| 4 | Control group (A) | 52 | 109 |
| 5 | Control group (A) | 61 | 87 |

cretion (related to body weight) and the urinary potassium excretion were similarly reduced in the test group (table III).

The derived mean postoperative urea clearance of the test group was also less than half that of the control group (table IV). Furthermore, there was a positive correlation ($r = 0.73$) between total body heat loss and postoperative urea clearance in patients sampled from both groups (fig. 1).

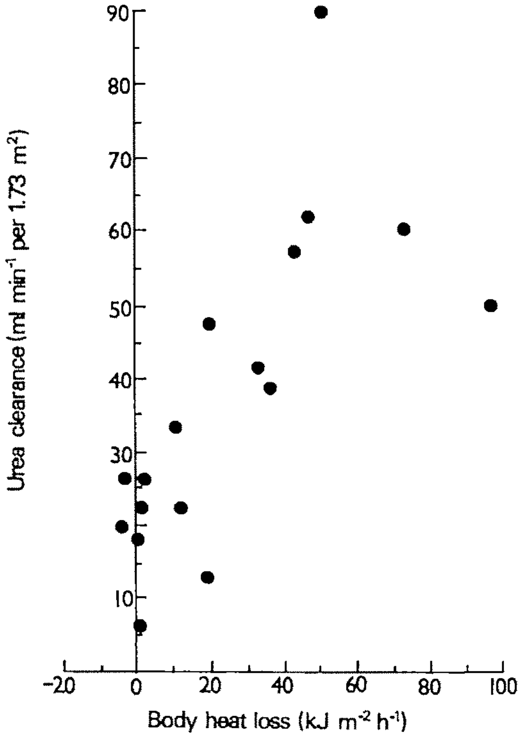

FIG. 1. Positive correlation between urea clearance and total body heat loss.

Heat loss was also positively correlated with the catabolic index (Bistrian, 1979) ($r = 0.66$) and urinary potassium excretion ($r = 0.65$) (table III).

The creatinine clearances measured after operation in five patients (table IV) showed the expected correlation with urea clearances over a wide range of values (Lubowitz et al., 1967; Lavender, Hilton and Jones, 1969) confirming that, in this study, the urea clearance was a valid approximation to the glomerular filtration rate.

## DISCUSSION

This study attempted to standardize patient age, operative procedure and environmental temperature to determine the changes which occur in body temperature and heat content in elderly patients during surgery and anaesthesia and how these changes can be modified. The mean skin temperature was determined using the four-point formula described by Ramanathan (1964). This method and the other 11 different formulae described by several authors, have been compared by Shanks (1975) with the 15-site reference value. The four-point formula was found to reach a 95% agreement to within 1 °C of the mean skin temperature during anaesthesia. Holdcroft and Hall (1978) compared the 15-site method of Mitchell and Wyndham (1969) with the four-point method during anaesthesia and recovery and found sufficient agreement.

The core temperature was recorded by an auditory canal probe chosen because it is well tolerated by the patient, easily inserted and does not cause trauma. Provided steps are taken to avoid draughts and cold air, aural canal temperature correlates well with oesophageal temperature (Holdcroft and Hall, 1978).

The results obtained are in agreement with those of Goldberg and Roe (1966) who described rapid cooling in patients older than 60 yr. The initial decrease in body temperature is marked during the first 0.5 h after induction of anaesthesia. During this time, there are large differences between the naked patient and the ambient theatre temperature and the skin is cleaned with cold liquids. After draping, the initial rapid decrease in temperature lessens. Average hourly heat loss was found in our study to be much greater in the unwarmed group A, but no correlation was found between the rate of decrease in core temperature and average hourly heat loss in either group. Vale (1973) has explained this is caused by redistribution of heat from the deep part of the body to the skin surface. Patients in whom all efforts were made to minimize heat loss (group B) showed stable heat content throughout the operation.

The measurement of urinary urea during the first 48 h after operation was used to establish the relationship between heat loss during operation and the catabolic response. The finding that reduction of body heat loss during operation resulted in substantially reduced nitrogen excretion in the test group is in accord with studies which showed a similar effect in animals (Cuthbertson and Tilstone, 1969; Cuthbertson, 1976) and in human subjects (Cuthbertson, Smith and Tilstone, 1968; Cuthbertson et al., 1972; Fleck, 1976) who were transferred to a warm environment immediately following trauma such as bone injury, burns or myocardial infarction.

However, Spivey and Johnston (1972) found no reduction in the nitrogen excretion of patients who were nursed at 29°C rather than 24°C following abdominal surgery. This would appear to be in contrast to results from the present study but, like the other series referred to, the warm environment was instituted after the trauma occurred and not, as in the present study, during the period of trauma itself. We are unaware of any previous metabolic study of this nature.

Spivey and Johnston (1972) suggested that the discrepancy of their findings with those of Cuthbertson, Smith and Tilstone (1968) might be caused by the relatively mild trauma and catabolic response of their patients compared with that of the bone injured patients of the latter authors. The difference in the severity of stress may be a further cause of discrepancy between their findings and the results in this study since the catabolic index (mean 12.1) of the control group corresponded to severe stress according to Bistrian (1979). A further difference is that the mean ages of our two groups were 70.8 and 76.8 yr compared with 46.4 and 44.1 yr in the corresponding groups of Spivey and Johnston (1972).

Mean urinary potassium excretion after operation in the test group was significantly less than in the control group, and combining data from both groups, there was a positive correlation between urinary potassium and urinary nitrogen excretion ($r = 0.80$) similar to that found by Cuthbertson and others (1972) on patients with bone trauma. These findings are consistent with the concept that post-traumatic energy requirement is provided, at least in part, by gluconeogenesis from amino acids derived from muscle catabolism (Cuthbertson et al., 1972; Cuthbertson, 1976) and that this energy production, which is directly related to nitrogen excretion (Cairnie et al., 1957; Cuthbertson, 1976) may be reduced in subjects who are maintained in a warm environment.

The mean urea clearance value after operation in the control group corresponded, on the basis of data from Lavender, Hilton and Jones (1969), to an inulin clearance of approximately 80 ml $\text{min}^{-1}$ which was similar to that found by Rush, Fishbeim and Wilder (1965) in a group of elderly postoperative patients.

In the test group, the mean urea clearance after operation was less than half that of the control group. This reduction in clearance was not associated with any increase in plasma urea concentration; on the contrary, the concentration was slightly, although not significantly, less, and it therefore seems unlikely that the reduced urea excretion of this group can be attributed only to reduced clearance. The data obtained are consistent with the concept that there was, in the test group, a reduction both in the generation of urea and the glomerular filtration rate compared with the corresponding values in the control group. No explanation can be offered for this latter observation, nor for the additional finding that overall, in both groups of patients, urea clearance was positively correlated with total body heat loss (fig. 1). The effect of warm ischaemia on renal function is well known (Whickham, Hanley and Joekes, 1967), but we are not aware of any study of the effects on renal function of small differences in temperature such as occurred in the present study. Some degree of renal ischaemia would be expected in the patients studied, because of anaesthesia itself (Bastion and Deutsch, 1976), and it may be that the relative warmth of the test group of patients was sufficient to cause the observed reduction in glomerular filtration rate which, as in other studies of more extreme conditions (Whickham, Hanley and Joekes, 1967) was manifest 24 h after the ischaemia. Further studies are needed, before and after operation, of renal, creatinine and urea clearances in order to confirm and clarify these findings.

It is therefore suggested that the attempt to minimize the metabolic effects of anaesthesia and surgery by maintaining the patient as far as possible in a thermoneutral environment, is alternative, or complementary, to extradural analgesia (Brandt et al., 1978) or high-dose fentanyl (Hall, 1980). Extradural analgesia and high-dose fentanyl, although effective, have a complication rate which may sometimes preclude their use, whereas prevention of heat loss is both beneficial and totally innocuous.

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REFERENCES

Allison, S. P. (1974). Metabolic aspects of intensive care. *Br. J. Hosp. Med.*, **11**, 860.

Bastion, R. D., and Deutsch, S. (1976). *Anaesthesia and the Kidney*. London: Academic Press.

Bay, J., Nunn, J. F., and Prys-Roberts, C. (1968). Factors influencing arterial $P_{O_2}$ during recovery from anaesthesia. *Br. J. Anaesth.*, **40**, 398.

Benzinger, T. H. (1969). Heat regulation homeostasis of central temperature in man. *Physiol. Rev.*, **49**, 671.

Bistrian, B. R. (1979). A simple technique to estimate severity of stress. *Surg. Gynaecol. Obstet.*, **148**, 675.

Boyan, C.P., and Howland, W. S. (1961). Blood temperature a critical factor in massive transfusion. *Anesthesiology*, **22**, 559.

Brandt, M., Fernandes, A., Mordhurst, R., and Kehlet, H. (1978). Epidural analgesia improves post-operative nitrogen balance. *Br. Med. J.*, **1**, 1106.

Burton, A. C., and Edholm, O. G. (1955). *Man in a Cold Environment*. London: Arnold.

Cairnie, A. B., Campbell, R. M., Pullar, J. D., and Cuthbertson, D. P. (1957). The heat production consequent on injury. *Br. J. Exp. Path.*, **38**, 504.

Colin, J., Timbal, J., Houdas, Y., Boutelier, C., and Guieu, J. D. (1971). Computation of mean skin temperature from rectal and skin temperatures. *J. Appl. Physiol.*, **31**, 484.

Cuthbertson, D. P. (1976). Surgical metabolism: historical and evolutionary aspects; in *Metabolism and the Response to Injury* (eds A. W. Wilkinson and D. P. Cuthbertson), p. 1. London: Pitman Medical.

—— Fell, G. S., Smith, C. M., and Tilstone, W. J. (1972). Metabolism after injury: effects of severity, nutrition and environmental temperature on protein, potassium, zinc and creatinine. *Br. J. Surg.*, **59**, 925.

—— Smith, C. M., and Tilstone, W. J. (1968). The effect of transfer to a warm environment (30 °C) on the metabolic response to injury. *Br. J. Surg.*, **55**, 513.

Cuthbertson, D. P., and Tilstone, W. J. (1969). Metabolism during the post injury period. *Adv. Clin. Chem.*, **12**, 1.

Dubois, D., and Dubois, E. F. (1915). The measurement of the surface area of man. *Arch. Int. Med.*, **15**, 358.

Dyde, J. A., and Lunn, H. F. (1970). Heat loss during thoractomy. *Thorax*, **25**, 355.

Editorial (1977). The old in the cold. *Br. Med. J.*, **1**, 336.

Fleck, A. (1976). The influence of the nature, severity and environmental temperature on the response to injury; in *Metabolism and the Response to Injury*, (eds A. W. Wilkinson and D. P. Cuthbertson), p. 44. London: Pitman Medical.

Goldberg, M. J., and Roe, C. F. (1966). Temperature changes during anesthesia and operations. *Arch. Surg.*, **93**, 365.

Hall, G. M. (1980). Fentanyl and the metabolic response to surgery. *Br. J. Anaesth.*, **52**, 561.

Holdcroft, A., and Hall, G. M. (1978). Heat loss during anaesthesia. *Br. J. Anaesth.*, **50**, 157.

Lavender, S., Hilton, P. J., and Jones, N. F. (1969). The measurement of glomerular filtration in disease. *Lancet*, **2**, 1216.

Lubowitz, H., Slatopalsky, E., Shankel, S., Rieselbach, R. E. and Bricker, N. S. (1967). Glomerular filtration rate. Determination in patients with chronic renal disease. *J.A.M.A.*, **199**, 100.

Mitchell, D., and Wyndham, C. H. (1969). Comparison of weighting formulas for calculating mean skin temperature. *J. Appl. Physiol.*, **26**, 616.

Morris, R. H. (1971). Operating room temperatures and the anesthetised paralysed patient. *Arch. Surg.*, **102**, 95.

Ramanathan, N. L. (1964). A new weighing system for mean surface temperature of the human body. *J. Appl. Physiol.*, **19**, 531.

Roe, C. F., Goldberg, M. J., Blair, C. S., and Kinney, J. M. (1966). Influence on early post-operative oxygen consumption. *Surgery*, **60**, 85.

Rush, B. F., Fishbeim, R., and Wilder, R. J. (1965). Effect of operative trauma upon renal function in older patients. *Ann. Surg.*, **162**, 863.

Shanks, C. A. (1975). Heat balance during surgery involving body cavity. *Anaesth. Intens. Care*, **3**, 114.

Smith, H. W. (1951). *The Kidney. Structure and Function in Health and Disease*. New York: Oxford University Press.

Spivey, J., and Johnston, I. D. A. (1972). The effect of environmental temperature and nutritional intake on the metabolic response to abdominal surgery. *Br. J. Surg.*, **59**, 93.

Vale, J. R. (1973). Normothermia: its place in operative and post-operative care. *Anaesthesia*, **23**, 241.

Whickham, J. E. A., Hanley, H. G., and Joekes, A. M. (1967). Regional renal hypothermia. *Br. J. Urol.*, **39**, 727.

## UNE ETUDE DES RELATIONS ENTRE LA PERTE CALORIQUE ET ET L'EXCRETION AZOTEE CHEZ LES SUJETS AGES SOUMIS A UNE CHIRURGIE ABDOMINALE MAJEURE SOUS ANESTHESIE GENERALE

### RESUME

Nous avons fait une tentative de réduction de la perte calorique chez des sujets agés soumis à une chirurgie abdominale majeure. Deux groupes ont été étudiés. Dans un groupe, des efforts pour minimiser la perte calorique ont été faits, en utilisant une

humidificateur chauffant sur le circuit d'anesthésie, un matelas à circulation d'au chaude placé sous le patient et un réchauffement de tous les liquides perfusés. Sinon les techniques anesthésique et chirurgicale étaient comparables. Dans tous les cas, la même technique anesthésique, associant le protoxyde d'azote, l'oxygène, le pancuronium et le fentanyl, avec une ventilation en pression positive intermittente, a été utilisée. L'excrétion azotée a été mesurée dans les urines recueillies pendant 48 h par l'intermédiaire d'une sonde urinaire à demeure mise en place peu après l'induction de l'anesthésie. La prévention des pertes caloriques pendant l'anesthésie et la période de réveil a entraîné une diminution significative de l'excrétion azotée.

## ERFORSCHUNG DES ZUSAMMENHANGS ZWISCHEN WÄRMEVERLUST UND STICKSTOFFAUSSCHEIDUNG BEI ÄLTEREN PATIENTEN, DIE SICH EINER GROßEN BAUCHOPERATION IN ALLGEMEINNARKOSE UNTERZIEHEN MUßTEN

### ZUSAMMENFASSUNG

Es wurde versucht, den Wärmeverlust bei älteren Patienten, die sich einer großen Bauchoperation unterziehen mußten, zu vermindern. Die Studie umfaßte zwei Gruppen. In der einen Gruppe bemühte man sich, den Wärmeverlust durch einen Heißwasser-Luftbefeuchter im Kreissystem, eine Unterlage mit zirkulierendem heißen Wasser und durch Erwärmung aller Infusionen niedrig zu halten. Ansonsten waren die chirurgischen und die Narkosetechniken vergleichbar. Lachgas in Sauerstoff, Pankuronium, Fentanyl und IPP-Beatmung wurden bei allen Narkosen verwendet. Sofort nach der Narkoseeinleitung wurde ein Blasenkatheter gelegt und die Stickstoffausscheidung wurde im Urin, der über 48 h gesammelt wurde, bestimmt. Die Vermeidung eines Wärmeverlustes während der Narkose und in der Aufwachphase führte zu einer signifikanten Verminderung des Stickstoffverlustes.

## UNA INVESTIGACIÓN RESPECTO DE LA RELACIÓN ENTRE LA PÉRDIDA DE CALOR Y LA EXCRECIÓN DE NITRÓGENO EN PACIENTES DE EDAD SOMETIDOS A CIRUJÍA ABDOMINAL MAYOR BAJO ANESTESIA GENERAL

### SUMARIO

Se intentó reducir la pérdida de calor en pacientes de edad sometidos a operaciones mayores de cirujía abdominal. Se estudiaron dos grupos. En un grupo, se hicieron esfuerzos para minimizar la pérdida de calor al usar un humectador de agua caliente en el circuito anestético, un colchón con sistema de circulación de agua caliente debajo del paciente y al calentar todos los fluidos i.v. Por otro lado, todas las técnicas anestéticas y quirúrgicas eran comparables. La misma técnica anestética con oxígeno, pancuronio y fentanilo y ventilación de presión positiva intermitente fue utilizada. La pérdida de nitrógeno fue medida en todos los casos, en la orina recuperada durante 48 h. de la sonda urinaria interior introducida de inmediato después de inducción de la anestesia. La prevención de pérdida de calor durante la anestesia y la recuperación post-operatoria tuvo por efecto una reducción significativa de la pérdida de nitrógeno.

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# CLINICAL COMPARISON OF THE BAIN AND MAGILL ANAESTHETIC SYSTEMS DURING SPONTANEOUS RESPIRATION

J. P. ALEXANDER

## SUMMARY

The Bain and Magill anaesthetic breathing systems were compared for spontaneous breathing during nitrous oxide in oxygen and halothane anaesthesia. A mean fresh gas flow ($\dot{V}$F) of 150 ml $kg^{-1}$ $min^{-1}$ (SD ± 30, range 106–250) was required with the Bain system to prevent rebreathing sufficient to cause respiratory stimulation; mean fresh gas flow/expired minute volume ($\dot{V}$F/$\dot{V}$E) was 1.49 (SD ± 0.32, range 0.86–2.17). Equivalent figures for the Magill attachment were a mean $\dot{V}$F of 82 ml $kg^{-1}$ $min^{-1}$ (SD ± 19, range 43 – 125), while mean $\dot{V}$F/$\dot{V}$E was 0.76, (SD ± 0.19, range 0.38–1.23, $P < 0.001$). The results attest the efficiency of the Magill attachment in terms of gas economics, and indicate the very high flows required to avoid respiratory stimulation in some subjects when the Bain system is used.

Although the Bain anaesthetic system, a co-axial version of the Mapleson D system, was described originally by Bain and Spoerel in 1972 there has been a lack of agreement as to the fresh gas flow required to maintain normocarbia in patients breathing spontaneously. The Mapleson D system is less efficient when compared with the Mapleson A system (Magill attachment) during spontaneous breathing, and fresh gas flows of between two and three times the patient's minute volume have been advocated (Mapleson, 1954). A number of studies have been undertaken (in conscious volunteers) to compare the efficiency of the two systems (Conway et al., 1976; Conway, Seeley and Barnes, 1977; Ungerer, 1978) and these indicated that acceptable concentrations of carbon dioxide could not be maintained unless hyperventilation occurred when fresh gas flow rates of less than 150 ml $kg^{-1}$ $min^{-1}$ of air were delivered through the Bain system.

Mansell (1976) noted gross hypercarbia in a spontaneously breathing anaesthetized patient when a fresh gas flow of 70 ml $kg^{-1}$ $min^{-1}$ was used. The present investigation was undertaken to compare the efficiency of the two systems in anaesthetized adult patients undergoing surgical operations, and to determine the amount of rebreathing and hyperventilation to be expected with varying gas inflows.

## PATIENTS AND METHODS

A preliminary series of experiments was undertaken in five healthy adult volunteers. Each subject received instruction to ensure normal breathing after correct application of a mouth-piece and nose-clip. Air was delivered from a compressor to either a Magill attachment or a Bain system via a pre-calibrated rotameter. Expired minute volume and carbon dioxide concentrations were measured as described below as the air flow was decreased stepwise from a maximum flow of 15 litre $min^{-1}$, by 1-litre steps at 4-min intervals, until obvious hyperpnoea occurred. The two systems were evaluated sequentially with a 20-min rest period between the experiments.

*Patients.* One hundred and three unpremedicated healthy adult male inpatients underwent oral surgery for the removal of impacted molars or exodontia. Mean ages and weights are shown in table I: all the patients weighed 50 kg or more. Anaesthesia was induced with methohexitone 1.5 mg $kg^{-1}$. Suxamethonium 1 mg $kg^{-1}$ was administered and a cuffed nasotracheal tube introduced. Anaesthesia was maintained with a mixture of 60% nitrous oxide in oxygen delivered from pre-calibrated rotameters, with the addition of 1–1.5% halothane vapour from a Fluotec vaporizer. Respiration was spontaneous throughout the study. The accuracy of the rotameters was checked on several occasions using a Series 1100 G.E.C. Marconi rotameter calibrated for air. Allowing for the increased density of 60% nitrous oxide in oxygen mixtures, and with suitable corrections for temperature and barometric pressure, readings were within 2% of predicted values at all flows between 3 and 16 litre.

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*Anaesthetic systems.* A single conventional Magill attachment, or commercial Bain system (Respiratory Care Inc.), was used throughout the study. The corrugated tubing of the former was 1.8 m long, and the reservoir bag had a capacity of 2 litre. The Heidbrink expiratory valve opened at a pressure 1 cm $H_2O$ greater than ambient pressure. The Bain system incorporated a similar expiratory valve and reservoir bag attached at the end distant from the patient.

*Carbon dioxide measurement.* Gas was extracted continuously at a rate of 200 ml $min^{-1}$ from a point close to the mouth and analysed for carbon dioxide concentration with an infra-red analyser (Godard Capnograph Mark 2) and the signals recorded. Preliminary experiments using known concentrations of carbon dioxide in both oxygen and 60% nitrous oxide in oxygen mixtures indicated that substitution of the latter for oxygen introduced a positive error of some 10% and that the addition of 1.5% halothane vapour decreased this error to 8% or less in the range 3–7% carbon dioxide. The error in this analyser was virtually negligible in the range 0–2% carbon dioxide (Russell, 1978). Since this investigation concentrated on rebreathing, only minimum inspired concentrations of carbon dioxide are considered.

*Ventilation.* Expired tidal volumes and minute volumes of ventilation were measured continuously with a pre-calibrated, direct-reading Wright electronic spirometer (B.O.C.) mounted at the patient end of the system. The instrument was tested for cyclical, intermittent gas flows using a calibration air syringe pumped at various rates. At the tidal volumes and respiratory rates obtained by the patients during the investigations, the spirometer over-read both tidal volumes and minute volumes by a maximum of 5% or less (Bushman, 1979). Since minute volume is measured at a temperature which is somewhere between body and ambient, no correction for temperature was made. Readings were recorded every 4 min and respiratory frequency was continuously recorded by the capnograph. Total deadspace for both systems was approximately 66 ml.

*Experimental programme.* Studies were carried out during surgery once the patients had settled into a steady breathing pattern. Observations were not made during periods of changing or intense surgical stimulation. The initial fresh gas flow was set at 14–16 litre $min^{-1}$ to prevent rebreathing. Occasionally, flows of up to 20 litre $min^{-1}$ were required when the Bain system was being evaluated. The gas mixture was adjusted to contain as near as possible 60% nitrous oxide, vith the addition of an extra 200 ml $min^{-1}$ of oxygen to compensate for the continuous extraction of gas by the capnograph. Gas flows were decreased stepwise by 1 litre $min^{-1}$ at 4-min intervals until evidence of rebreathing was indicated by the presence of carbon dioxide in the inspired gas mixture. Stepwise decreases in gas flow were continued until hyperventilation occurred. If a decrease in flow to less than 4 litre $min^{-1}$ was required, this was achieved in 0.5-litre steps. When hyperventilation occurred, further decreases in gas flow were undertaken in some subjects to ascertain by how much respiratory minute volume could increase.

Criteria for rebreathing and increased ventilation were taken as an increase in minute volume or tidal volume of 5% or more not accompanied by a decrease in minimum inspired carbon dioxide concentration, or an increase in minimum inspired carbon dioxide concentration of at least 0.2%.

Altogether, 24 patients were studied while breathing through the Bain system, and a further 24 using the Magill attachment. The remaining 55 patients, whose operations took at least 1 h to complete, were anaesthetized using both systems. Once studies were completed with one, the alternative system was connected to the subject, and a high gas flow was provided for 10 min. At the end of this time, it was established in all patients that minute ventilation and minimum inspired carbon dioxide values had decreased to basal values, and measurements were then repeated. Selection of the system to be evaluated first was random. Twenty-nine subjects breathed through the Magill attachment initially, followed by the Bain, while in the remaining 26 the reverse order was followed. Particular note was made of the gas flow used before, and the minimum inspired carbon dioxide concentration present when respiratory stimulation occurred. The results were analysed in these 55 patients using a paired Student's *t* test, and in the other 48 patients using an unpaired *t* test (Olivetti P 602 micro-computer).

## RESULTS

In the preliminary experiments involving conscious volunteers, rebreathing was demonstrated in all five subjects when the Bain system was used with a flow of 15 litre $min^{-1}$, confirming the findings of Conway, Seeley and Barnes (1977) and of Ungerer (1978). In two subjects this flow was not sufficient to prevent hyperventilation. The mean gas flow required to avoid hyperventilation was therefore greater than 215 ml $kg^{-1}$ $min^{-1}$, corresponding to a fresh gas flow/expired minute volume ratio ($\dot{V}$F/$\dot{V}$E) of more than 1.36. Equivalent figures for the Magill attachment were 116 ml $kg^{-1}$ $min^{-1}$ fresh gas flow and a $\dot{V}$F/$\dot{V}$E ratio of 0.84. Respiratory frequency increased in all subjects when respiratory stimulation occurred, and further decreases in fresh gas flow led to minute volumes which were more than three times resting volumes in two subjects.

In the anaesthetized patients, rebreathing occurred at high gas flows when the Bain system was in use. Further increases in both inspired carbon dioxide concentration and minute ventilation indicated that respiratory stimulation occurred as fresh gas flow was decreased. For simplification, $F_{ICO_2(min)}$ refers to the minimum carbon dioxide concentration recorded at the mouth during inspiration (table I). In the majority of patients, respiratory rate remained constant, and there was no difficulty in determining the point at which minute ventilation increased. A few patients, however, had poor responses to carbon dioxide loads, with only a small increase in ventilation in spite of further decreases in gas flow.

Mean $\dot{V}$F/$\dot{V}$E ratio for patients using the Magill attachment only was 0.76, corresponding to a fresh gas flow of 78 ml $kg^{-1}$ $min^{-1}$. Values for patients who breathed via the Bain system only were $\dot{V}$F/$\dot{V}$E ratio of 1.50 and mean fresh gas flow of 148 ml $kg^{-1}$ $min^{-1}$. The mean increases in minute volume when hyperventilation occurred were 32% and 30% respectively (range 7–86%).

Almost identical results were obtained in the patients who breathed via both systems sequentially

TABLE I. *Number of anaesthetized subjects in each study (mean ± SD) (range in parentheses) of age, weight, fresh gas flow ($\dot{V}$F) and fresh gas flow/expired minute volume ratio ($\dot{V}$F/$\dot{V}$E) before hyperpnoea occurred, and the increase in $\dot{V}$E and minimum inspired carbon dioxide concentration (%) ($F_{ICO_2(min)}$) when hyperpnoea was first evident. Unpaired* t *test between (a) and (e):* t = *8.506,* P < *0.001; paired* t *test between (d) and (h)* t = *16.633,* P < *0.001*

| No. | Age (yr) | Weight (kg) | $\dot{V}$F (ml $kg^{-1}$ $min^{-1}$) | $\dot{V}$F/$\dot{V}$E | Increase in $\dot{V}$E (%) | $F_{ICO_2(min)}$ |
|---|---|---|---|---|---|---|
| MAGILL ATTACHMENT | | | | | | |
| (a) Magill only | | | | | | |
| 24 | 27±11 | 71±10 | 78±17 | 0.76±0.21 | 32±21 | 0.6±0.4 |
| | (15–62) | (53–97) | (53–116) | (0.44–1.2) | (10–86) | (0.2–2.0) |
| (b) Magill before Bain | | | | | | |
| 29 | 27±13 | 71±13 | 85±20 | 0.79±0.19 | 38±22 | 0.6±0.3 |
| | (13–55) | (50–100) | (55–125) | (0.38–1.23) | (5–100) | (0.2–1.4) |
| (c) Magill after Bain | | | | | | |
| 26 | 27±10 | 68±11 | 79±19 | 0.72±0.19 | 19±11 | 0.7±0.4 |
| | (15–62) | (50–93) | (43–120) | (0.40–1.17) | (6–53) | (0.2–1.4) |
| (d) Total breathing through Magill before and after Bain (sum of (b) and (c)) | | | | | | |
| 55 | 27±11 | 70±12 | 82±19 | 0.76±0.19 | 29±20 | 0.6±0.3 |
| | (13–62) | (50–100) | (43–125) | (0.38–1.23) | (5–100) | (0.2–1.4) |
| BAIN SYSTEM | | | | | | |
| (e) Bain only | | | | | | |
| 24 | 25±8 | 71±8 | 148±35 | 1.50±0.37 | 30±18 | 2.0±0.5 |
| | (15–43) | (50–110) | (88–220) | (0.86–2.17) | (7–83) | (1.0–2.8) |
| (f) Bain before Magill | | | | | | |
| 26 | as at (c) above | | 154±40 | 1.50±0.33 | 38±21 | 2.2±0.6 |
| | | | (106–250) | (0.92–2.11) | (14–90) | (1.0–3.8) |
| (g) Bain after Magill | | | | | | |
| 29 | as at (b) above | | 143±22 | 1.49±0.33 | 25±13 | 1.9±0.5 |
| | | | (108–208) | 1.0–2.2 | (6–69) | (1.0–3.2) |
| (h) Total breathing through Bain before or after Magill (sum of (f) and (g)) | | | | | | |
| 55 | as at (d) above | | 150±30 | 1.49±0.32 | 31±18 | 2.0±0.6 |
| | | | (106–250) | (0.86–2.17) | (6–90) | (1.0–3.8) |

(table I), although somewhat smaller increases in respiratory minute volume were observed when hyperventilation occurred at the completion of the second set of observations, suggesting that perhaps an element of fatigue may influence the behaviour of the respiratory centre, although a more likely explanation is that the operation was nearing completion and surgical stimulation was decreasing.

## DISCUSSION

Rebreathing is present when the mixed inspired gas reaching the alveoli contains a concentration of carbon dioxide which is greater than that accounted for by the alveolar gas re-inhaled from the patient's anatomical deadspace. Using this criterion, the results presented here verify the findings of others (Conway, Seeley, and Barnes, 1977; Ungerer, 1978) that, when patients respire through the Bain system, rebreathing occurs at almost all conventional flow rates. Minor degrees of rebreathing, however, may not be of any importance, since it is only at the stage where rebreathing constitutes a sufficient carbon dioxide load to cause respiratory stimulation that hyperventilation occurs. The conscious subjects required mean fresh gas flows of more than $215\,\text{ml kg}^{-1}\,\text{min}^{-1}$ to avoid hyperventilation. The efficiency of the Magill attachment was confirmed; mean fresh gas flows less than 0.9 times minute volume were sufficient to avoid respiratory stimulation in both awake and anaesthetized subjects. Experiments performed on awake subjects breathing air are not necessarily applicable to anaesthetized patients since metabolic rate and carbon dioxide production may be less in the latter, and the response to a carbon dioxide challenge obtunded. Comroe (1965) stated that an atmosphere containing 1% carbon dioxide would increase respiratory minute volume by an average of 1 litre in normal man.

Information about the concentration of carbon dioxide required to produce respiratory stimulation in anaesthetized patients is hard to find. Adriani (1962) considered that concentrations of 0.5% or greater were unacceptable, while Jorgensen and Jorgensen (1973) thought that 0.6% should not be exceeded in a circle absorber system. Spoerel, Aitken and Bain (1978), in a study on 101 healthy young dental outpatients, claimed that spontaneous breathing via the Bain system was safe, and that a fresh gas flow could be selected which would allow maintenance of a normal arterial carbon dioxide tension ($Pa_{CO_2}$) without undue respiratory effort. They claimed that a fresh gas flow of $100\,\text{ml kg}^{-1}\,\text{min}^{-1}$ would increase respiratory minute volume by 20%, an almost identical response to that which they observed when using the Magill attachment with a fresh gas flow of $70\,\text{ml kg}^{-1}\,\text{min}^{-1}$. Using the Bain system with a fresh gas flow of $70\,\text{ml kg}^{-1}\,\text{min}^{-1}$, the same authors reported a mean increase in respiratory minute volume of 57%.

Table I shows that, in this investigation, when significant rebreathing occurred, the initial mean increase in respiratory minute volume was of the order of 30–40%. However, the response in any individual was totally unpredictable, ranging from 5 to 100% and some patients had only a limited response even when fresh gas flows were decreased to obviously inadequate values. Indeed, only five patients were able to double minute ventilation under these circumstances, although this effect was not sought in all patients.

The effects of surgical stimulation on respiration are well known, although the mechanism is not altogether clear (Lam, Clement and Knill, 1980). This stimulation does not necessarily improve the activity of chemical reflexes, or improve compensation to rebreathing, and there may be additional factors to take into account, such as increases in catecholamine concentration, metabolic rate, carbon dioxide production, and changes in cardiac output. These workers found an average increase in ventilation of 30% during periods of intense surgical stimulation, but a decrease in $Pa_{CO_2}$ of only 10%. Kain and Nunn (1968) predicted that under conditions of rebreathing, $Pa_{CO_2}$ would be controlled by the fresh gas flow rather than by alveolar ventilation.

Conway and colleagues (1976) found that when ventilation increased in conscious volunteers, carbon dioxide output increased and led to a greater disparity between fresh gas flow and alveolar ventilation. An increase in the work of breathing will obviously increase carbon dioxide production (Conway, 1976). The effects of surgical stimulation and anaesthetic duration on ventilatory compensation are negligible at low fresh gas flow rates when compared with the effect of the inspired carbon dioxide load. Abnormal patterns of breathing, changes in deadspace volume/tidal volume ($\dot{V}_D/\dot{V}_T$) ratios and altered I:E ratios may all lead to decreases in the efficiency of gas exchange (Willis, Pender and Mapleson, 1975). These workers found that a fresh gas flow of twice the minute volume was necessary to eliminate rebreathing completely in a Mapleson F system (the Jackson–Rees modification of Ayre's T-piece), and that there was an increase of only

10–20% in respiratory minute volume at fresh gas flows of 1.5 times normal ventilation. Conscious volunteers may increase their minute volume by 300% or more during rebreathing, with a considerable increase in respiratory rate. As noted, the response in anaesthetized patients was greatly reduced. These patients invariably had a tachypnoea resulting from halothane, and seldom increased their respiratory rate further in response to rebreathing. Some seemed almost incapable of increasing their ventilation, a feature noted by Byrick (1980a), who classified his patients as good or poor responders. The same worker (Byrick, 1980b) noted that the fresh gas flow needed to abolish rebreathing was highly variable and was dependent on respiratory waveform. The very brief expiratory pause during halothane anaesthesia results in an increase in the entrainment of carbon dioxide per breath from the expiratory limb of the Bain system. Because of the lower respiratory rate with enflurane anaesthesia, lower fresh gas flows could be used before rebreathing occurred. This is not necessarily advantageous since the greater ventilatory depression seen with the latter drug inevitably leads to greater $Pa\text{CO}_2$ values during anaesthesia. Knill and Gleb (1978) found that halothane at concentrations of 1.1 MAC decreased the response to hypercapnoea by more than 50%.

The package insert for the Bain system recommends a fresh gas flow of 100 ml $\text{kg}^{-1}$ $\text{min}^{-1}$ for adult patients breathing spontaneously. The data presented here indicate that this is patently inadequate and that, in the *average* patient, a fresh gas flow of 150 ml $\text{kg}^{-1}$ $\text{min}^{-1}$ will be just adequate to avoid hyperventilation. However, the range is wide, depending on carbon dioxide production, the requirements being greatest in young adults and, in particular, teenagers. One patient in this study required a fresh gas flow of 250 ml $\text{kg}^{-1}$ $\text{min}^{-1}$ to prevent hyperventilation. Rose, Byrick and Froese (1978) felt that fresh gas flows of 200–300 ml $\text{kg}^{-1}$ $\text{min}^{-1}$ were necessary to prevent rebreathing, and emphasized the possible danger to an individual patient in any group being obscured if only grouped data are analysed. There is no evidence available to support the suggestion that hyperventilation is beneficial.

## REFERENCES

Adriani, J. (1962). The *Chemistry and Physics of Anesthesia*, 2nd edn, p. 168. Springfield, Illinois: Thomas.

Bain, J. A., and Spoerel, W. E. (1972). A streamlined anaesthetic system. *Can. Anaesth. Soc. J.*, 19, 426.

Bushman, J. A. (1979). Effect of different flow patterns on the Wright respirometer. *Br. J. Anaesth.*, 51, 895.

Byrick, R. J. (1980a). Respiratory compensation during spontaneous ventilation with the Bain circuit. *Can. Anaesth. Soc. J.*, 27, 96.

——(1980b). Respiratory waveform and rebreathing in T-piece circuits. *Anesthesiology*, 53, 371.

Comroe, J. H. (1965). *Physiology of Respiration*, p. 59. Chicago: Year Book Medical Publishers Incorporated.

Conway, C. M. (1976). A theoretical study of gaseous homeostasis in the Magill circuit. *Br. J. Anaesth.*, 48, 441.

——Davis, F. M., Knight, H. J., Leith, J. M., Preston, T. D., and Tennant, R. (1976). An experimental study of gaseous homeostasis and the Magill circuit using low fresh gas flows. *Br. J. Anaesth.*, 48, 447.

——Seeley, H. F., and Barnes, P. K. (1977). Spontaneous ventilation with the Bain anaesthetic system. *Br. J. Anaesth.*, 49, 1245.

Jorgensen, B., and Jorgensen, S. (1973). Carbon dioxide elimination from circle systems. *Acta Anaesthesiol. Scand.*, (Suppl.) 53, 86.

Kain, M. L., and Nunn, J. F. (1968). Fresh gas economics of the Magill circuit. *Anesthesiology*, 29, 964.

Knill, R. L., and Gleb, A. W. (1978). Ventilatory responses to hypoxia and hypercapnia during halothane sedation and anesthesia in man. *Anesthesiology*, 49, 244.

Lam, A. M., Clement, J. L., and Knill, R. L. (1980). Surgical stimulation does not enhance ventilatory chemoreflexes during enflurane anaesthesia in man. *Can. Anaesth. Soc. J.*, 27, 22.

Mansell, W. H. (1976). Spontaneous breathing with the Bain circuit at low flow rates: a case report. *Can. Anaesth. Soc. J.*, 23, 432.

Mapleson, W. W. (1954). The elimination of rebreathing in various semi-closed anaesthetic systems. *Br. J. Anaesth.*, 26, 323.

Rose, D. K., Byrick, R. J., and Froese, A. B. (1978). Carbon dioxide elimination during spontaneous ventilation with a modified Mapleson D system: studies in a lung model. *Can. Anaesth. Soc. J.*, 25, 353.

Russell, W. J. (1978). The effect of nitrous oxide on an infrared carbon dioxide analyser. *Anaesth. Intens. Care*, 6, 167.

Spoerel, W. E., Aitken, R. R., and Bain, J. A. (1978). Spontaneous respiration with the Bain breathing circuit. *Can. Anaesth. Soc. J.*, 25, 30.

Ungerer, M. J. (1978). A comparison between the Bain and Magill anaesthetic systems during spontaneous breathing. *Can. Anaesth. Soc. J.*, 25, 122.

Willis, B. A., Pender, J. W., and Mapleson, W. W. (1975). Rebreathing in a T-piece: volunteer and theoretical studies of the Jackson–Rees modification of Ayre's T-piece during spontaneous respiration. *Br. J. Anaesth.*, 47, 1239.

## UNE COMPARAISON CLINQIUE DES SYSTEMES ANESTHESIQUES DE BAIN ET DE MAGILL EN VENTILATION SPONTANEE

### RESUME

Les circuits anesthésiques respiratoires de Bain et de Magill ont été comparés pour la ventilation spontanée au cours d'une anesthésie au protoxyde d'azote dans-oxygène et holothane. Le circuit de Bain nécessitait un débit moyen de gaz frais ($\dot{V}_F$) de

150 ml kg$^{-1}$ min$^{-1}$ (DS ± 30, valeurs extrêmes 106–250) pour prévenir un rebreathing suffisant pour entraîner une stimulation respiratoire. Le rapport entre débit moyen de gaz frais et débit expiré ($\dot{V}_F/\dot{V}_E$) était 1,49 (DS ± 0,32, valeurs extrêmes 0,86–2,17). Les chiffres correspondants pour le circuit de Magill étaient un $\dot{V}_F$ moyen de 82 ml kg$^{-1}$ min$^{-1}$ (DS ± 19, valeurs extrêmes 43–125) tandis que le $\dot{V}_F/\dot{V}_E$ moyen était 0,76 (DS ± 0,19, valeurs extrêmes 0,38–1,23, $P < 0{,}001$). Ces résultats attestent l'efficacité du circuit de Magill en matière d'économie de gaz et montrent les débits très élevés nécessaires chez certains sujets pour éviter la stimulation respiratoire quand le circuit de Bain est utilisé.

## EIN KLINISCHER VERGLEICH DES BAIN- UND MAGILL-NARKOSESYSTEMS BEI SPONTANATMUNG

### ZUSAMMENFASSUNG

Das Bain- und Magill-Narkosesystem wurde für Spontanatmung verglichen während Lachgas-Sauerstoff-Halothannarkose. Ein mittlerer Frischgasflow ($\dot{V}\mathrm{F}$) von 150 m kg$^{-1}$ min$^{-1}$ (SD ± 30, Bereich 160–250) war beim Bain-System erforderlich daß die Atmung ungenügend war, um eine Stimulierung der Atmung zu bewirken. Der mittlere Quotient Frischgasflow zum áusgeatmeten Minutenvolumen ($\dot{V}\mathrm{F}/\dot{V}\mathrm{E}$) war 1,49 (SD ± 0,32, Bereich 0.86–2,17). Äquivalente Werte für das Magill-System waren ein mittlerer $\dot{V}\mathrm{F}$ von 82 ml kg$^{-1}$ min$^{-1}$ (SD ± 19, Bereich 43–125), während das mittlere $\dot{V}\mathrm{F}/\dot{V}\mathrm{E}$ 0,76 war (SD ± 0,19, Bereich 0,38–1,23, $P < 0{,}001$). Die Ergebnisse bestätigen die Wirksamkeit des Magill-Systems, was ökonomischen Umgang mit Gasen betrifft, und weisen auf die hohen Flows hin, die erforderlich sind, um die Stimulierung der Atmung bei einigen Patienten zu verhindern, wenn das Bain-System verwendet wird.

## COMPARACIÓN CLÍNICA DE LOS SISTEMAS DE ANESTESIA BAIN Y MAGILL DURANTE LA RESPIRACIÓN ESPONTÁNEA

### SUMARIO

Se llevó a cabo una comparación de los sistemas respiratorios anestéticos Bain y Magill para respiración espontánea durante la anestesia por óxido nitroso en oxígeno y halotano. Se necesitó una corriente media de gas fresco ($\dot{V}\mathrm{F}$) de 150 mg kg$^{-1}$ min$^{-1}$ (SD ± 30, escala 106–250) con el sistema Bain con el objeto de impedir una nueva respiración suficiente como para provocar un estímulo respiratorio; la relación corriente media de gas fresco/volumen-minuto expirado ($\dot{V}\mathrm{F}/\dot{V}\mathrm{E}$) era de 1,49 (SD ± 0,32, escala 0,86–2,17). Las cifras correspondientes del aparato Magill representaban un $\dot{V}\mathrm{F}$ medio de 82 ml kg$^{-1}$ min$^{-1}$ (SD ± 19, escala 43–125), mientras que la relación promedia $\dot{V}\mathrm{F}/\dot{V}\mathrm{E}$ era de 0,76 (SD ± 0,19, escala 0,38–1,23, $P < 0{,}001$). Los resultados comprueban la eficacia del aparato Magill en términos de economía de gas e indican las muy altas corrientes necesarias para impedir el estímulo respiratorio en algunos sujetos cuando se usa el sistema Bain.

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# LUMBAR SYMPATHETIC AND COELIAC PLEXUS BLOCKS
## *An anatomical study in cadavers*

D. A. CHERRY AND D. M. RAO

## SUMMARY

Percutaneous coeliac plexus and lumbar sympathetic blocks were performed "blind" in cadavers to investigate the frequency of puncture of a major organ. In a series of 120 needle placements, the kidney was punctured on only one occasion and this would almost certainly have been prevented by the use of fluoroscopy. The proximity of the needles to the lumbar sympathetic chain support the efficacy of this technique.

The frequency of puncture of a major organ, in particular the kidney, during coeliac plexus block has been reported recently to be greater than believed previously (Moore, Bush and Bennett, 1981). Since the method of performing lumbar sympathetic blockade percutaneously is not dissimilar (Reid, Watt and Gray, 1970), similar possibilities exist.

Needles were inserted "blind" to the regions of the coeliac plexus and lumbar sympathetic chain in 20 cadavers to determine what major structures were punctured, and to assess how precisely the needles had been placed in relation to the lumbar sympathetic chain.

## MATERIALS AND METHODS

The technique of inserting the needles was based on that described by Reid, Watt and Gray (1970). Only cadavers which were about to be subjected to postmortem were used, and no mutilating procedures were undertaken.

With the cadaver in the lateral position, three 22-gauge, 15-cm needles were inserted approximately 10 cm (4 in) from the midline at the approximate levels of L1, L2 and L3. In thin cadavers the distance of insertion of the needles from the midline was less, approximately 7.5 cm, while in obese subjects the distance was greater (up to 12.5 cm).

Each needle was advanced on to the vertebral body, gradually positioned more anteriorly until it slipped beyond the antero-lateral aspect of the vertebral body and then advanced to the "hilt" to allow the cadaver to be positioned supine. The cadaver was then rolled over and the performance repeated on the other side.

The most cephalad needle was inserted just caudal to the most inferior rib and advanced cephalad at an angle of 15° to allow the needle to pass close to the upper border of the L1 vertebral body, as is our custom when performing these blocks in clinical practice.

## RESULTS

Eighty needles were inserted in the direction of the lumbar sympathetic chain and 95% passed either through the lumbar sympathetic chain or within 0.5 cm of it. In 90% of those occasions on which the chain was not traversed, the needles were lateral to the chain.

One needle passed through the hilum of the kidney, although in that cadaver there was a large osteophyte over an intervertebral disc which displaced the needle laterally. Two needles were found embedded in grossly osteoporotic vertebral bodies.

Of the 40 coeliac plexus "blocks", three needles were found in the pleural space, although the lung itself did not seem to have been punctured. The position of these needles varied considerably in level in relation to the vertebral body and it was only on those occasions on which the needle had coursed more cephalad than had been intended that puncture of the pleura occurred. We hope that under fluoroscopic control this complication would be very rare.

## DISCUSSION

On only one occasion, a "lumbar sympathectomy", did the needle pass through a kidney, and this would doubtless have been prevented by using a C-arm Image Intensifier as is used routinely in clinical

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practice during coeliac plexus and lumbar sympathetic blockade. The siting of some of the needles in the pleura and in the vertebral bodies would also, in all probability, have been avoided by using image intensification. The position of the lumbar sympathetic chain was found to be remarkably constant on the anterolateral aspect of the vertebral column. Almost all the needles passed either through the sympathetic chain or lateral to it. The high frequency of the proximity of the needle to the sympathetic chain support the efficacy of this block. As figure 1 shows, the more lateral the insertion of the needle, the closer the tip should be to the lumbar sympathetic chain.

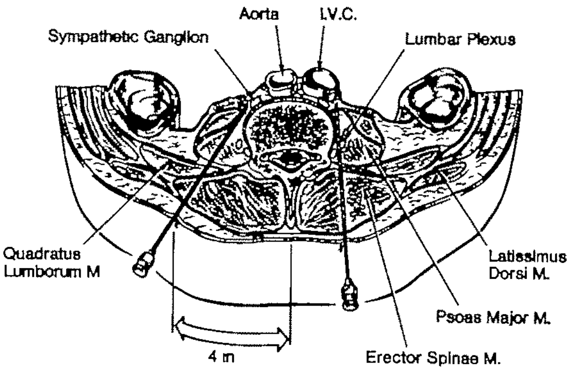

FIG. 1. The rationale for the more lateral approach to the lumbar sympathetic chain.

No attempt was made to halt the advance of the needles beyond the lumbar sympathetic chain or coeliac plexus because of the nature of the investigation. However, in patients, this is done using the loss of resistance technique and confirmed by the spread of non-phenol containing CONRAY 280 and fluoroscopy.

In these cadavers, although the genito–femoral nerve was found to emerge from the psoas muscle at variable levels it was usually below L3 (bearing in mind that it was difficult to be certain of the exact vertebral body level). Having emerged, the nerve occasionally ran more medially than some text books would have us believe.

One could postulate that so-called post-sympathectomy neuralgia is, in fact, a neuralgia of the genito–femoral nerve, and by keeping the sympathectomy above the middle of L3 and preventing any lateral spread of the 10% phenol–dye mixture by the lateral insertion of the needles, the frequency of post-sympathectomy neuralgia might be decreased.

It is recommended that a mobile image intensifier is used when performing these blocks. It seems difficult to justify, from our experience, the time and expense of a CT scan. In only one instance was the kidney punctured and the variation in these results from those described by Moore, Bush and Bennett (1981) is unlikely to be accounted for by the use of cadavers in the present study.

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REFERENCES

Moore, D. C., Bush, W. H., and Bennett, L. L. (1981). Coeliac plexus block: a roentgenographic, anatomic study of technique and spread of solution in patients and corpses. *Anesth. Analg. (Cleve.)*, **60**, 369.

Reid, W., Watt, K. J., and Gray, T. G. (1970). Phenol injection of the sympathetic chain. *Br. J. Surg.*, 57, 45.

## BLOCS DES PLEXUS SYMPATHIQUE, LOMBAIRE ET COELIAQUE. *UNE ETUDE ANATOMIQUE SUR LE CADAVRE.*

### RESUME

Nous avons pratiqué des blocs percutanés des plexus lombaire, sympathique et coeliaque "a l'aveugle" sur des cadavres pour étudier la fréquence des ponctions d'un organe noble. Dans une série de 120 ponctions, le rein n'a été ponctionné qu'une seule fois et cet accident aurait presque certainement été prévenu par l'usage dela fluoroscopie. Les aiguilles étaient très proches de la chaine sympathique lombaire, ce qui corrobore l'efficacité de cette technique.

## LUMBALE BLOCKADE DES SYMPATHISCHEN UND ZÖLIAKALEN PLEXUS,

### *EINE ANATOMISCHE STUDIE AN LEICHEN*

### ZUSAMMENFASSUNG

Die perkutane lumbale Blockade des Plexus coeliacalis und sympaticus wurde an Leichen blind durchgeführt, um das Auftreten der Punktion eines größeren Organes zu untersuchenk. In einer Reihe von 120 Nadelplazierungen wurde nur bei einer Gelegenheit die Niere punktiert. Dies wäre fast sicher durch die Verwendung der Fluoroskopie vermieden worden. Die Nähe der Nadeln zu den lumbalen Sympatikusganglien betonen die Wirksamkeit dieser Technik.

## BLOQUEOS DEL PLEXO CELÍACO Y DEL SIMPÁTICO LUMBAR

### *Un estudio anatómico en cadáveres*

### SUMARIO

Se llevaron a cabo bloqueos percutáneos del simpático lumbar y del plexo celíaco "a ciegas" en cadáveres, con el objeto de investigar la frecuencia de perforación de un órgano mayor. En una serie de 120 colocaciones de aguja, se perforó una sola vez el riñón y al usar la fluoroscopia, se hubiera evitado eso con casí certidumbre. La proximidad de las agujas para con la cadena simpática lumbar apoya la eficacia de dicha técnica.

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# PATTERN OF RESPIRATION IN PATIENTS RECOVERING FROM BARBITURATE OVERDOSE

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## SUMMARY

Ventilation has been recorded in seven patients who were unconscious following self-poisoning. Measurements were obtained on admission to the hospital and repeated daily until the patients regained consciousness. On admission, recordings were characterized by a low minute ventilation as a result of a low tidal volume in spite of a high frequency of respiration. During the period of recovery tidal volume and minute ventilation increased, whereas frequency decreased. The modifications observed during recovery were the reverse of those noted during the induction of anaesthesia with barbiturates in man. However, these modifications differ from those observed during induction of anaesthesia in cats. Consequently, as far as respiratory control is concerned, models elaborated in animals cannot be extrapolated to deeply anaesthetized human subjects.

Anaesthesia affects the pattern of breathing differently in man and in experimental animals. In animals, a decrease in the frequency of respiration is associated with small and variable changes in tidal volume, whereas in man, frequency of respiration is increased and the tidal volume is decreased (Gautier and Gaudy, 1978). Obviously these divergent effects of anaesthesia can be attributed to the differences between species. However, another hypothesis should be considered and such a consideration has initiated the present study. In physiological studies on animals anaesthesia is deep and long-lasting. In contrast, ventilatory studies carried out in man are often undertaken before, or immediately following, a minor surgical procedure which has been carried out under light anaesthesia of short duration. Thus, it could be that the differences in the pattern of breathing referred to above result from the deeper level of anaesthesia in the animals.

Recordings of respiratory activity are difficult to obtain and of poor quality during light anaesthesia in animals because of spontaneous movements and defence reactions. On the other hand, it is unethical deliberately to deepen the level of anaesthesia in man to study the possible changes in ventilatory pattern. Therefore, we have tested our hypothesis in patients presenting in deep coma after the self-administration of drugs. Respiratory activity was monitored repeatedly until consciousness was regained. In the present work, we present results from patients poisoned principally with barbiturates particularly, since the literature on the effects of such a situation on ventilatory activity is scanty (Sybrecht et al., 1979).

## PATIENTS AND METHODS

*Patients.* Of 15 patients admitted, following self-poisoning, to the Intensive Care Unit of the Hospital St Antoine and whose ventilation was monitored, seven (four females and three females) were selected for inclusion in the study according to the following criteria: (1) ingestion of a large dose of barbiturates confirmed by measurement of the blood concentration on admission (18–95 mg litre$^{-1}$). A mixture of barbiturates and other hypnotics was sometimes found. (2) Deep coma on admission with absence of any response to noxious stimuli which persisted for at least 24 h and allowed us to perform at least two recordings. (3) Absence of documented lung or neurological diseases.

On admission to the hospital an endotracheal tube was inserted and the lungs ventilated mechanically (rate 15 b.p.m., tidal volume 10–15 ml kg$^{-1}$, and $F_{IO_2} = 0.30$). In addition to routine clinical management, blood-gas tensions and the concentrations of blood sugar, BUN and electrolytes were measured. Chest x-ray and e.e.g. were carried our regularly. Forced diuresis (3 litre of physiological saline per day) was undertaken. Patients older than 40 yr received heparin 10 mg i.v. every 2 h.

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*Measurements.* Once or twice each day, the patient was disconnected from the ventilator and flow measured (Fleisch No. 1 pneumotachograph and Statham transducer). After integration of the flow signal the respiratory trace and the airflow were recorded on a Hewlett–Packard recorder at a speed of 25 mm $s^{-1}$. Calibration of the pneumotachograph was performed at the end of the recording using a calibrated syringe. Recordings were carried out usually in ambient air. However, in six of the patients, they were also performed with 100% oxygen on 19 occasions. On these occasions, 100% oxygen was administered during the 5 min of mechanical ventilation preceding disconnection from the respirator.

During those recordings performed shortly after admission to the hospital, apnoea was often observed when the patients were connected to the pneumotachograph. If this lasted for 3–4 min or if, at any time, the physician found it necessary, the patient was reconnected to the ventilator. Recordings were performed until the respiratory trace became regular; this generally occurred within 5 min after starting to record.

Recordings of respiratory activity were carried out until the patients recovered consciousness such that they could not tolerate the endotracheal tube and showed irregular breathing patterns. The time between the first and the last recordings varied between 1 and 7 days in the different patients.

*Analyses of recordings.* Five to 10 consecutive respiratory cycles were analysed from each recording. Analyses consisted of measurement of the durations of inspiration and expiration and measurement of tidal volume and from these average frequency of respiration and minute ventilation were computed for each recording. The Student's *t* test for paired samples was used to evaluate significance.

## RESULTS

*Initial recordings.* The first recording of respiratory activity was characterized by fast and shallow breathing: average value for tidal volume was 0.167 ± 0.025 litre (range 0.077–0.260 litre) and for frequency, 25.2 ± 2.2 b.p.m. (range 19.5–33.7 b.p.m.). The resulting minute ventilation reached 3.974 ± 0.445 litre $min^{-1}$ (fig. 1).

Analysis of the respiratory trace showed that, on average, the duration of inspiration (1.22 ± 0.08 s) did not differ significantly from that of expiration (1.27 ± 0.14 s) (fig. 2). Indeed, in three of the seven patients, the duration of inspiration exceeded the duration of expiration.

At the time of the first recording, body temperature was low: 35.3 ± 0.9 °C. Arterial blood-gas tensions analysed during mechanical ventilation preceding the first recording showed $Pa_{O_2}$ = 14.7 ± 2.7 kPa, $Pa_{CO_2}$ = 3.3 ± 0.3 kPa and pH 7.53 ± 0.03 unit.

*Further recordings.* These were characterized by modifications in the respiratory trace such that, when the first and last recordings were compared, a significant increase was observed in tidal volume (average increase being 0.185 ± 0.030 litre, $P < 0.001$) and a decrease in the frequency of respiration was noted in six of the seven patients (average decrease for the group 4.5 ± 1.9 b.p.m.). As a result, minute ventilation increased by 3.0 ± 0.6 litre $min^{-1}$ ($P < 0.01$). The average changes in ventilatory pattern between first and last recording are depicted in

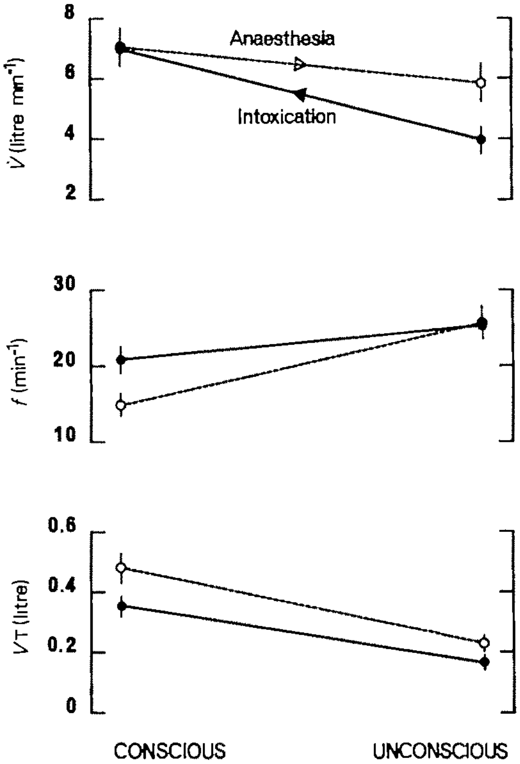

FIG. 1. Average values (± SEM) of tidal volume ($V_T$), breathing frequency (*f*) and minute ventilation ($\dot{V}$) of seven unconscious subjects for the first recording on admission to the hospital and for the last recording after they regained consciousness (solid line). Also shown, the values obtained in a group of five subjects before and during anaesthesia with barbiturates (broken line).

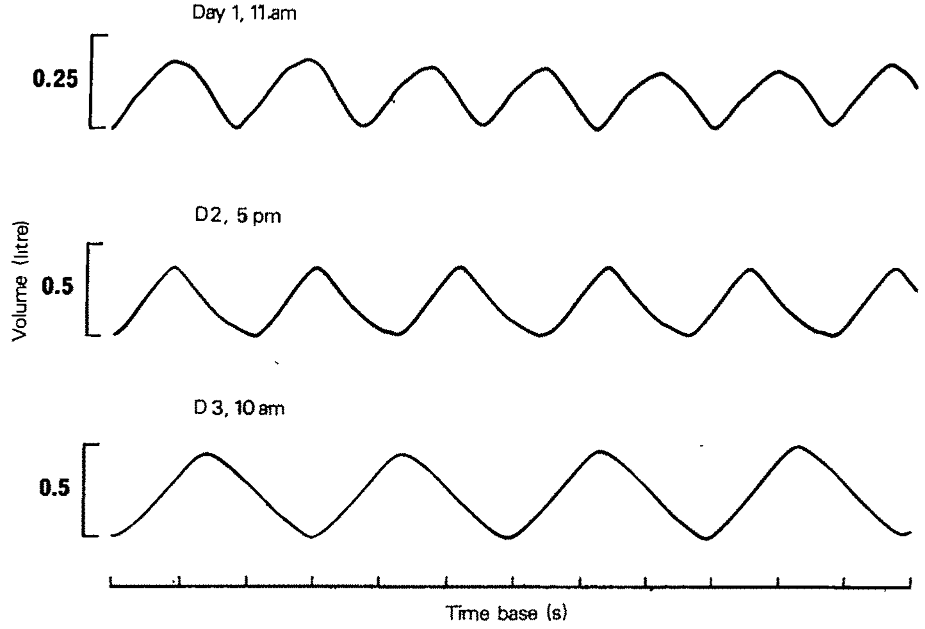

FIG. 2. Respiratory wave form (inspiration upward) in an unconscious subject on admission to the hospital, then 1 and 2 days later. The subject was conscious when the last recording was performed.

figure 1, which shows also the average values obtained in five subjects before and during anaesthesia using barbiturates (Gautier and Gaudy, 1978). It seems remarkable that changes in tidal volume, frequency and minute ventilation were similar in both groups of subjects. Day-to-day changes in breathing pattern for a typical subject are shown in figure 3.

In the six patients who breathed pure oxygen before and during the recording of respiratory activity, no consistent changes in breathing pattern were noted when compared with breathing ambient air. Average values in air were: 1.20±0.05 s for the duration of inspiration, 1.34±0.08 s for the duration of expiration and 0.233±0.018 litre for tidal volume. In oxygen, the values were: 1.25±0.06 s, 1.34±0.11 s and 0.237±0.023 litre respectively.

## DISCUSSION

The results of the present work show that, as patients suffering from barbiturate poisoning regain consciousness, their minute ventilation increases as a result of an increase in tidal volume which is greater than the decrease in the frequency of ventilation. These changes occur in a direction which was the reverse of those observed when a conscious

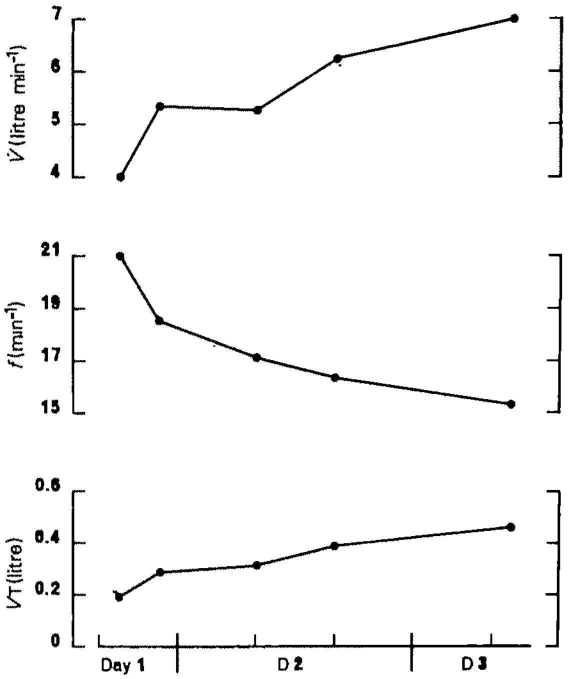

FIG. 3. Changes in tidal volume ($V_T$), breathing frequency ($f$) and minute ventilation ($\dot{V}$) of a typical subject during recovery of consciousness.

subject is anaesthetized (fig. 1), although the time course is different: a few minutes in the case of anaesthesia and up to several days following overdose. It should be emphasized that the changes in ventilation, although related to the elimination of the drug, can also be affected by other factors:

(1) During the recovery from overdose body temperature increased by 1.5–2.0 °C and would increase metabolism and, therefore, ventilation.

(2) Respiratory activity was not recorded during a totally steady-state. The analyses of the respiratory patterns were made several minutes after stopping mechanical ventilation, which had induced slight hyperventilation. Furthermore, the ventilatory activity characterized by a low tidal volume and high frequency, observed in the initial recordings, would have been followed by alveolar hypoventilation, had not the patients been reconnected to the respirator. This was particularly likely since the ventilatory response to hypercapnia has been shown to be impaired in similar patients (Sybrecht et al., 1979). For ethical and practical reasons, we did not repeat the analysis of arterial blood-gas tensions in this transient period, but the fact that breathing oxygen did not consistently change the breathing pattern, suggests that hypoxia was not responsible for the relatively high respiratory rate.

(3) Poisoning was sometimes caused by a mixture of barbiturates and other hypnotics, particularly benzodiazepines which may modify respiratory activity *per se* (Rao et al., 1973; Clarke and Lyons, 1977). These mixed drug overdoses may partially account for both the variability of the results and the varying duration of unconsciousness.

(4) It should be noted that, in the last measurements, frequency of respiration was still high (around 20 b.p.m.) and tidal volume relatively low (less than 0.4 litre). This pattern may be accounted for partly by the agitation noted in several conscious patients who were unable to tolerate the endotracheal tube by this stage.

Although the ventilatory changes which are associated with the recovery from poisoning differ, to some extent, from those induced by anaesthesia because of the factors considered above, it appeared from the present results that they are relatively similar. The ventilatory changes induced by anaesthesia are well described (Severinghaus and Larson, 1965; Munson et al., 1966; Derenne et al., 1976; (Gautier and Gaudy, 1978) whereas changes associated with an overdose of hypnotics have been studied much less. In unconscious patients poisoned with various hypnotics, Sybrecht and colleagues (1979) observed changes in respiratory mechanics and in the ventilatory response to hypercapnia which were identical to those observed during anaesthesia (Derenne et al., 1976). As far as ventilatory pattern was concerned, Sybrecht and coworkers (1979) mention that in one patient, frequency of respiration was markedly slower when the patient was conscious. On the other hand, the pattern of ventilation has been studied in unconscious patients with head injury or after an acute cerebrovascular event. North and Jennett (1974) and Leigh and Shaw (1976) noted that in these patients respiration was rapid and was often associated with hyperventilation. Although anaesthetized subjects, or those presenting with barbiturate overdose may differ from such patients, it seems noteworthy that in both forms of unconsciousness an increase in the frequency of respiration was observed.

The present study confirms our previous work showing that, in contrast to animals, man has a faster respiratory rate when anaesthetized than when conscious. This difference does not seem to be caused by a different level of anaesthesia, since in the present study the patients were so depressed by the drug that mechanical ventilation was required for several days before regaining consciousness. A species difference is likely, since in a recent publication it was observed that the Breuer–Hering reflex which terminates inspiration is also different in anaesthetized humans and cats (Gautier, Bonora and Gaudy, 1981).

Besides the relative tachypnoea and hypoventilation demonstrated by the patients, other modifications of respiratory pattern were similar to those observed during anaesthesia. The mean inspiratory flow ($V_T/T_I$) which reflects the activity of the inspiratory centre (Milic-Emili and Grunstein, 1976) increased during the period of awakening from 136 ± 18 to 267 ± 22 ml $s^{-1}$ ($P < 0.01$) and the duty cycle (ratio of duration of inspiratory to duration of total breath ($T_I/T_{tot}$) which reflects the timing of the respiratory activity) decreased from 0.49 ± 0.02 to 0.44 ± 0.01 ($P < 0.02$). These modifications observed in humans are the only changes which were similar to those observed in cats (Gautier, 1976; Webber and Peiss, 1979), suggesting that anaesthesia has some similar effects on respiratory activity in different animal species.

In conclusion, deeply anaesthetized human subjects present several characteristic modifications of respiratory activity. These differ from those observed in anaesthetized animals such as the cat, which is often used to elaborate models of the control of respiratory activity. This work does not allow us to explain the origin of these differences. However, it serves to emphasize that the extrapolation to man, of models of the control of respiratory activity based on experiments carried out on animals, even under anaesthesia, should be cautious.

### REFERENCES

Clark, R. S. J., and Lyons, S. M. (1977). Diazepam and flunitrazepam as induction agents for cardiac surgical operations. *Acta Anaesthesiol. Scand.*, 21, 282.

Derenne, J. P., Couture, J., Iscoe, S., Whitelaw, W. A., and Milic-Emili, J. (1976). Occlusion pressures in men rebreathing $CO_2$ under methoxyflurane anesthesia. *J. Appl. Physiol.*, 40, 805.

Gautier, H. (1976). Pattern of breathing during hypoxia or hypercapnia of awake or anesthetized cat. *Respir. Physiol.*, 27, 193.

—— Bonora, M., and Gaudy, J. H. (1981). Breuer–Hering inflation reflex and breathing pattern in anesthetized man and cat. *J. Appl. Physiol.*, 51, 1162.

—— Gaudy, J. H. (1978). Changes in ventilatory pattern induced by intravenous anesthetic agents in human subjects. *J. Appl. Physiol.*, 45, 171.

Leigh, R. J., and Shaw, D. A. (1976). Rapid regular respiration in unconscious patients. *Arch. Neurol.*, 33, 356.

Milic-Emili, J., and Grunstein, M. M. (1976). Drive and timing components of ventilation. *Chest*, (Suppl.), 70, 131.

Munson, E. S., Larson, C. P. jr, Badad, A. A., Regan, M. J., Buechel, D. R., and Eger, E. I. II. (1966). The effects of halothane, fluroxene and cyclopropane on ventilation: a comparative study in man. *Anesthesiology*, 27, 716.

North, J. B., and Jennett, S. (1974). Abnormal breathing patterns associated with acute brain damage. *Arch. Neurol.*, 31, 338.

Rao, S., Sherbaniuk, R. W., Prasad, K., Lee, S. J. K., and Sproule, B. J. (1973). Cardiopulmonary effects of diazepam. *Clin. Pharmacol. Ther.*, 14, 182.

Severinghaus, J. W., and Larson, C. P. jr (1965). Respiration in anaesthesia; in *Handbook of Physiology, Respiration* Vol. II, (eds W. O. Fenn and H. Rahn), p. 1219. Washington D.C.: American Physiological Society.

Sybrecht, G. W., Taubner, E. M., Bohm, M. M., and Fabel, H. (1979). Mechanical properties of the respiratory system and mouth-occlusion pressure in patients acutely intoxicated with hypnotics. *Lung*, 156, 49.

Webber, C. L. jr, and Peiss, C. N. (1979). Pentobarbital-induced apneusis in intact, vagotomized, and pneumotaxic-lesioned cats. *Respir. Physiol.*, 38, 37.

## MODE DE VENTILATION DES SUJETS EN PHASE DE RECUPERATION D'UN COMA BARBITURIQUE

### RESUME

La ventilation de sept patients dans le coma, à la suite d'une absorption volontaire de barbituriques, a été enregistrée. Les enregistrements ont été fait à l'arrivée à l'hôpital et répétés quotidiennement jusqu'au retour à une conscience normale. A l'admission, les enregistrements étaient caractérisés par une ventilation minute faible due à un faible volume courant malgré une fréquence respiratoire rapide. Pendant la phase de récupération, le volume courant et la ventilation minute augmentaient tandis que la fréquence diminuait. Les modifications observées au cours de la phase de récupération étaient l'inverse de celles observées lors de l'induction d'une anesthésie par les barbituriques chez l'homme. Cependant, ces modifications diffèrent de celles observées lors de l'induction de l'anesthésie chez le chat. Par conséquent, pour tout ce qui concerne le contrôle de la ventilation, les modèles élaborés chez l'animal ne peuvent être extrapolés aux êtres humains profondément anesthésiés.

## ATEMMUSTER VON PATIENTEN, DIE SICH VON EINER BARBITURAT-ÜBERDOSIS ERHOLEN

### ZUSAMMENFASSUNG

Die Atmung von sieben Patienten, die bewußtlos waren, nachdem sie sich selbst vergiftet hatten, wurde aufgezeichnet. Die Messungen wurden nach der Einlieferung in das Krankenhaus begonnen und täglich fortgesetzt, bis die Patienten das Bewußtsein wiedererlangt hatten. Bei der Einlieferung waren die Atemwerte durch ein niedriges Atemminutenvolumen gekennzeichnet, das durch ein niedriges Atemzugvolumen zustandekam, obwohl die Atemfrequenz hoch war. Während der Erholungsperiode nahm das Atemzugvolumen und das Minutenvolumen zu, während die Frequenz abnahm. Die während der Erholungsphase zu beobachtenden Veränderungen waren das Gegenstück von jenen, die während der Narkoseeinleitung mit Barbituraten beim Menschen zu beobachten sind. Diese Veränderungen unterscheiden sich jedoch von denen, die bei Katzen beobachtet wurden. Folglich können, was die Atemkontrolle betrifft, die bei Tieren ausgearbeiteten Modelle nicht auf Menschen in tiefer Narkose übertragen werden.

## TIPO DE RESPIRACIÓN EN PACIENTES QUE SE RECUPERAN DE UNA SOBREDOSIS DE BARBITÚRICOS

### SUMARIO

En siete pacientes que se encontraban inconscientes después de un autoenvenenamiento, se tomó registros de la ventilación. Se consiguieron mediciones al momento de su admisión en el hospital y se repitieron diariamente hasta que los pacientes volviesen en sí. Al admitirlos, los registros fueron caracterizados por una ventilación respiratoria baja a raíz del bajo volumen respiratorio a pesar de una alta frecuencia de respiración. Durante el periodo de recuperación, el volumen y la ventilación respiratorios aumentaron mientras que bajaba la frecuencia. Las modificaciones observadas durante la recuperación eran opuestas a las que se advierten durante la inducción de anestesia por barbitúricos en el hombre. Sin embargo, dichas modificaciones difieren de las observadas durante la inducción de la anestesia en los gatos. Por consiguiente, en lo que se refiere al control respiratorio, no se pueden extrapolar los modelos elaborados en los animales a los sujetos humanos profundamente anestesiados.

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# PERIOPERATIVE CHANGES IN COMPLEMENT ASSOCIATED WITH CARDIOPULMONARY BYPASS

H. BORALESSA, J. A. SHIFFERLI, F. ZAIMI, E. WATTS, J. G. WHITWAM AND A. J. REES

## SUMMARY

The total haemolytic complement ($CH_{50}$), the complement components C3 and C4, the complement breakdown product C3d, alternative pathway activation and transferrin, were measured before, during and after cardiopulmonary bypass. As expected, $CH_{50}$ decreased after heparinization, remained low during bypass and decreased further up to 8 h after bypass. C3 and C4 decreased significantly during bypass, continued to decrease for a further 8 h after bypass (by 35% and 40% respectively) and thereafter increased gradually up to 48 h. Although the depletions observed were suggestive of complement activation, there were no demonstrable increases in C3d, and in all patients the concentration of C3d remained within the normal range. Hence it was concluded that complement depletions of this magnitude were unlikely to result from complement activation. Non-specific changes in protein concentrations during bypass, as a result of dilution, redistribution or other unidentified factors, are more probable causes of the observed reductions. The acute phase response to surgery may be a factor in the subsequent increase in C3 and C4 which is seen 24 h after bypass. As transferin concentrations in the plasma are known to decrease during this response the observed decrease in transferrin concentration would support this view.

The potent peptides C3a and C5a which are released when complement is activated are thought to contribute to the pulmonary dysfunction which sometimes follows cardiopulmonary bypass (CPB) and to the pathogenesis of the post perfusion syndrome (Chenoweth et al., 1981). Both C3a and C5a are known to stimulate release of histamine from mast cells and to cause an increase in vascular permeability (Hugli, 1979) which is a feature of the post-perfusion syndrome (Kirklin, 1980). In addition, plasma C5a concentrations have been shown to be increased in the adult respiratory distress syndrome (ARDS) (Hammerschmidt et al., 1980) where similar organ dysfunction is seen. The demonstration of complement activation by crossed immunoelectrophoresis (Haslam, Townsend and Branthwaite, 1980) and the generation of C3a and C5a during bypass (Chenoweth et al., 1981) suggested that these fragments could contribute to the postoperative complications associated with CPB. However, despite the generation of C3a and C5a the patients studied had no clinical symptoms which could be related to those of active complement fragments either during bypass or in the period after operation.

The present study was undertaken to measure the degree of complement activation during cardiopulmonary bypass by using C3d as an indicator of such activation. Unlike previous studies (Chenoweth et al., 1981) observations were continued up to 48 h after the procedure. In addition, transferrin was used as a protein marker.

## METHODS

### *Patients and surgical procedures*

Ten male patients undergoing elective coronary artery bypass surgery were studied. Their mean age was 48 yr (range 32–60 yr, SD 9 yr). Premedication consisting of papaveretum 20 mg, hyoscine 0.4 mg and droperidol 5 mg, was administered i.m. 90 min before arrival in the induction area. Anaesthesia was induced with thiopentone 250–300 mg i.v. and papaveretum 6 mg i.v., followed by pancuronium 10 mg i.v. and after intubation was maintained with 67% nitrous oxide in oxygen, incremental doses of papaveretum to a total dose of $1\ mg\ kg^{-1}$ body weight and a further dose of pancuronium 4 mg during bypass. The mean arterial pressure was maintained in the range 70–80 mm Hg throughout, before bypass with halothane and after bypass with sodium nitroprusside. Surgery consisted of a me-

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dian sternotomy and placement of four reversed segments of autogenous saphenous vein grafts from the coronary arteries to the aorta.

Cardiopulmonary bypass equipment was standard and comprised an American Optical Pump, and Bentley BOS 10 bubble oxygenator. Cardiotomy filters were used. The pump oxygenator system was primed with Hartmann solution 2500 ml and sodium bicarbonate 25 mmol. After the administration of bovine lung heparin 300 i.u. $kg^{-1}$, bypass was instituted with an initial flow rate of 2.4 litre $min^{-1}$ per $m^2$ body surface area. During CPB the patients were cooled to 26–28 °C and flow rates were reduced to 1.4 litre $min^{-1}$ $m^{-2}$. After aortic cross clamping, myocardial preservation was maintained with 1–1.5 litre of cardioplegia (St Thomas's) solution. After the coronary arterio–venous anastomoses were performed the cross clamp was removed and the aorta–venous anastomoses performed, during which time the patient was gradually rewarmed and resumption of cardiac activity occurred spontaneously.

The lungs were ventilated with 50% oxygen in nitrogen 1.5 litre $min^{-1}$ throughout bypass. Total bypass time varied between 1 h 10 min and 1 h 30 min.

Potassium was administered to maintain a concentration of approximately 4.5 mmol $litre^{-1}$ throughout. After removal of the perfusion cannulae protamine was administered in a dose of 1 mg per 300 units of heparin. Coagulation was measured using an automated activated clotting time (Hemochron). At the end of surgery the patients returned to the intensive care unit and were ventilated in the period immediately after operation. Ventilation was terminated and the trachea extubated 4–8 h after surgery. The patients were discharged from hospital 8–10 days later and remained well during this period.

All these patients received 2–3 units of 3–5 day old CPD blood in the period immediately after bypass and after operation a further 1–2 units was administered to restore the haematocrit to normal.

### *Collection of samples*

Samples of venous blood were collected at the times shown in table I for complement assays. Two aliquots of blood were taken. One sample was placed in EDTA for C3d estimation and the other allowed to clot to measure C3, C4, $CH_{50}$, alternative pathway activity and transferrin. The cells were separated by centrifugation, and the plasma or serum was separated and stored at −70 °C. The assays were performed in a single batch.

TABLE I. *Times at which samples of venous blood were collected for complement assays*

| Sample | Time |
|---|---|
| 1 | 24 h before surgery |
| 2 | After induction of anaesthesia but before surgery |
| 3 | After administration of heparin |
| 4 | 10 min after institution of CPB |
| 5 | 20 min after institution of CPB |
| 6 | 30 min after institution of CPB |
| 7 | 60 min after institution of CPB |
| 8 | After administration of protamine |
| 9 | 1 h after termination of CPB |
| 10 | 4 h after termination of CPB |
| 11 | 8 h after termination of CPB |
| 12 | 24 h after termination of CPB |
| 13 | 48 h after termination of CPB |

### *Complement measurements*

Total haemolytic activity ($CH_{50}$) and alternative pathway function were measured as described by Lachmann and Hobart (1978) and the results were expressed as a percentage of the value from a pool of five samples of normal human serum.

Plasma C3 and C4 were measured by single radial immunodiffusion and the results were expressed as a percentage of a pool of five normal human sera.

C3d was measured by the technique of Perrin, Lambert and Miescher (1975).

All concentrations were corrected for dilution relative to the preoperative haemoglobin concentrations during bypass and in the periods after bypass and after operation using the formula:

$$\text{Corrected concentration} = \frac{\text{Measured concentration} \times \text{initial PCV}}{\text{PCV at time of measurement}}$$

### *Transferrin measurement*

An automated, immunoprecipitation assay (Technicon) was used to measure serum transferrin.

## RESULTS

No complications were observed in the patients studied during bypass or in the period after operation.

### *$CH_{50}$*

A significant decrease in $CH_{50}$ ($P < 0.05$) was seen after heparinization compared with the value before

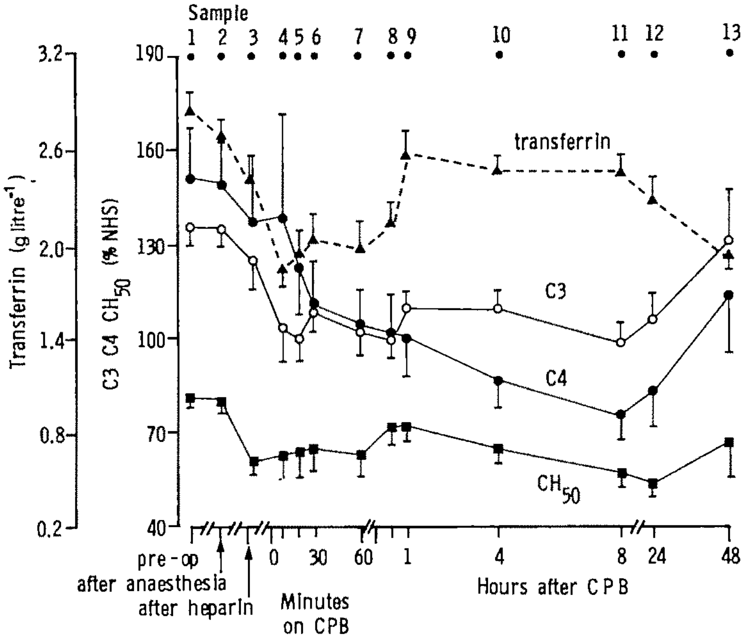

FIG. 1. Total haemolytic complement ($CH_{50}$), C3, C4 and transferrin concentrations in the plasma before, during and after cardiopulmonary bypass in 10 patients (mean ± SEM). NHS = normal human serum.

operation (fig. 1). Thereafter no further reduction of $CH_{50}$ values occurred up to 60 min on bypass. $CH_{50}$ was significantly reduced at 4 h ($P<0.05$), 8 h ($P<0.005$) and 24 h ($P<0.0005$) after bypass (table II).

Haemolytic alternative pathway activity showed changes similar to those in $CH_{50}$ but these were not significant (table II).

### *C3d*

C3d concentrations did not change during the period of study and for all patients remained in the normal range ($<2.05\ \mu g\ ml^{-1}$).

### *C3 and C4*

No significant difference was seen between the values of C3 and C4 before operation and their values before bypass. Ten minutes after commencing cardiopulmonary bypass, C3 concentration decreased in all 10 patients ($P<0.005$) and thereafter remained reduced up to 60 min. In contrast, C4 decreased gradually during bypass and at 60 min was seen to be reduced in all 10 patients ($P<0.0005$).

C3 and C4 continued to decline up to 8 h after the termination of bypass. Thereafter, C3 and C4 concentrations increased gradually (fig. 1); however, 24 h after bypass they were still significantly less ($P<0.005$) than the values before operation (table II).

### *Transferrin*

No differences were seen between the transferrin concentrations before operation and those after heparinization, (table II). Ten minutes after commencing CPB the plasma transferrin concentration decreased in all 10 patients. The mean concentration was reduced to 69% of the value before operation ($P<0.005$) (fig. 1). Unlike C3 and C4, transferrin concentrations returned to normal within 1 h after bypass. Thereafter a slow continuous decrease was observed up to 48 h.

## DISCUSSION

The present study demonstrated a reduction in the concentration of C3 and C4 not only during cardiopulmonary bypass (CPB) but also in the period after bypass, an observation which has not been made in previous studies which terminated early in the postoperative period (Hammerschmidt et al., 1981). An important observation made in other studies (Chenoweth et al., 1981) is that, despite complement changes, no substantial complications were seen in the patients studied and this was also

TABLE II. *Complement and transferrin assays (mean ± SD in units specified). NHS = normal human serum; AP = haemolytic alternative pathway. Tests of significance:* $^{*}P < 0.05$; $^{**}P < 0.005$; $^{***}P < 0.0005$. *Normal ranges: (% NHS) C4 60–140, C3 60–140,* $CH_{50}$ *50–150, AP 50–150; (g litre*$^{-1}$*) transferrin 1.5–3.0*

| | Before CPB | | CPB | | After CPB | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 24 h pre-op. | After heparin | 10 min | 60 min | 1 h | 4 h | 8 h | 24 h | 48 h |
| C3 (% NHS) | 136±15 | 126±17 | 103±33** | 107±21** | 109±15** | 110±15*** | 99±19*** | 106±24** | 131±57 |
| C4 (% NHS) | 151±54 | 137±67 | 139±103 | 111±48*** | 103.8±39*** | 87±29*** | 76±35*** | 84±39** | 114±55 |
| Transferrin (g litre$^{-1}$) | 2.68±0.5 | 2.42±0.4 | 1.8±0.3** | 1.9±0.3*** | 2.6±0.4 | 2.5±0.2 | 2.48±0.25 | 2.36±0.3 | 1.43±0.35** |
| C3:transferrin ratio | 50.7 | 52.0 | 57.2 | 56.3 | 41.9 | 44 | 39.9 | 44.9 | 68.2 |
| $CH_{50}$ (% NHS) | 80±10 | 61±13 | 62±22 | 64±21 | 71±11 | 65±13* | 57±13** | 53±13*** | 67±28 |
| AP (% NHS) | 85±17 | 90±26 | 93±41 | 108±45 | 101±25 | 93±26 | 78±24 | 78±21 | 85±37 |

true for the patients in the present study.

The relatively large values of C3 and C4 before operation in these patients could be explained by low values in the standard pool used for the control assays. Alternatively, all the patients were suffering from heart disease and since C3 and C4 are acute phase reactants, the initial values could be expected to be increased in some of these patients.

All the protein concentrations including C3 and C4 were corrected for dilution and since all of them showed a decrease during bypass, it could be assumed that they were all part of a process which may be common to many proteins during bypass. The return of transferrin to pre-bypass concentrations immediately after bypass when C3 and C4 continued to decrease suggests that the reduction in complement concentration after bypass reflects a more specific process. However, as there was no increase in the C3 breakdown product C3d during this period, despite a 40% decrease in complement concentration, it was concluded that complement activation was unlikely to be the cause of this reduction.

Freezing and rewarming blood for complement assays does not cause complement activation *in vitro* (Garratty, 1970). The failure to demonstrate an increase in C3d in the present study suggests that hypothermia, with temperatures of 28 °C, does not cause complement activation.

Heparin blocks complement activation (Loos, Volkanis and Stroud, 1976; Raepple, Hill and Loos, 1976) and the decrease in $CH_{50}$ is in keeping with this. Heparin protamine complexes activate the classical complement pathway (Lachman and Hobart, 1978), but the absence of an increase in C3d suggests that these did not cause persistent significant activation in the present study.

C3 and C4 are well preserved in CPD stored blood (Schifferli et al., 1982). Thus in those patients in whom the C3 and C4 concentrations were reduced by 30% and 40%, the 2–3 units of 3–5 day old blood which they received in the period immediately after bypass would tend to increase the concentrations of C3 and C4.

The complement concentrations in blood represent a dynamic equilibrium between synthesis, degradation and distribution into various body compartments, for example intravascular and extravascular. The changes observed could be attributable to any or all of these factors. The reductions in concentration of C3 and C4 observed during bypass were unlikely to be a result of reduced synthesis as they occurred too rapidly. However, reduced synthesis could contribute to the further reduction seen after operation as the fractional catabolic rates of C3 and C4 are 1.71%$h^{-1}$ and 1.4%$h^{-1}$ respectively (Ruddy et al., 1976). Clinical and experimental studies show that some proteins are denatured when exposed to cardiopulmonary bypass equipment. For example Pruitt, Stroud and Scott (1971) have shown, *in vitro*, that gammaglobulins when exposed to the oxygenator pump system undergo denaturation and precipitation with albumin and that the tendency to form such precipitates increases at lower temperatures. Two studies support the view that this denaturation could also occur *in vivo*. First, significant reductions of immunoglobulins were seen in patients after CPB (Parker et al., 1972), but not after other surgical procedures (Hairston et al., 1969). Second, anti-gammaglobulin antibodies have been demonstrated in the sera of patients who have undergone surgery with CPB (Pretty et al., 1968). Thus it is conceivable that complement proteins could be similarly denatured without the production of C3d. For instance, the altered complement proteins could bind to erythrocytes, similar to C3c binding to red cells seen during storage of blood (Szymanski and Odgren, 1979); or C3 and C4 *per se* could bind to red cells as a result of physicochemical changes related to bypass, similar to the way in which C3 and C4 bind to red cells when physicochemical alterations are produced *in vitro* (Heier, Kornstad and Nordhagen, 1981).

Although complement activation during bypass has been demonstrated in several studies (Chenoweth et al., 1981) the patients did not have any clinical complications which could be related to such activation either during or after surgery, which suggests that the degree of complement activation was insufficient to produce complications. Haslam, Townsend and Branthwaite (1980) demonstrated complement activation by two-dimensional immunoelectrophoresis, not only in patients undergoing cardiopulmonary bypass, but also in patients undergoing thoracotomy without bypass and hence did not provide any real evidence that complement activation is a feature peculiar to bypass. Furthermore, changes in complement were not quantified and hence this study also fails to give any indication of the degree of complement depletion. The demonstration by Chenoweth and his associates (1981) of the appearance of complement fragments C3a and C5a during bypass is conclusive evidence of complement activation. However, whilst C3a in plasma was shown to increase progressively during bypass, the concentration subsequently decreased after bypass, which is not consistent with continuous activation. This finding is in complete accordance with the present study which failed to demonstrate increased generation of C3d after CPB and justifies the conclusion that the increasing reduction in C3 and C4 seen after bypass in the present study is not related to activation. Moreover, Chenoweth and his associates inferred C5a production by demonstrating increased leucocyte receptor occupancy by this fragment. However, their patients remained clinically well and they did not show an increase in the plasma concentrations of C5a which is the case in patients with organ dysfunction (Hammerschmidt et al., 1980).

Whereas during cardiopulmonary bypass some complement activation can be detected by sensitive assays (Chenoweth et al., 1981), the continuing reduction in C3 and C4 concentrations seen after bypass in this study were shown to be unrelated to activation; neither did the patients studied have any clinical complications. It was concluded that the observed changes in C3 and C4 were probably related to some other unidentified mechanism which merits further investigation.

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REFERENCES

Chenoweth, D. E., Cooper, S. W., Hugli, T. E., Stewart, R. W., Blackstone, E. H., and Kirklin, J. W. (1981). Complement activation during cardiopulmonary bypass: evidence for generation of C3a and C5a anaphylatoxins. *N. Engl. J. Med.*, **304**, 497.

Garratty, G. (1970). Effects of storage and heparin on the activity of serum complement, with particular reference to the detection of blood group antibodies. *Am. J. Clin. Pathol.*, **54**, 531.

Hairston, P., Manes, J. P., Graber, C. D., and Lee, W. H. (1969). Depression of immunologic surveillance by pump oxygenation perfusion. *J. Surg. Res.*, **9**, 587.

Hammerschmidt, D. E., Stroncek, D. F., Bowers, T. K., Lammi-Keefe, C. J., Kurth, D. M., Ozalins, A., Nicoloff, D. M., Lillehei, R. C., Craddock, P. R., and Jacob, H. S. (1981). Complement activation and neutropenia occurring during cardiopulmonary bypass. *J. Thorac. Cardiovasc. Surg.*, **81**, 370.

—— Weaver, L. J., Hudson, L. D., Craddock, P. R., and Jacob, H. S. (1980). Association of complement activation and elevated plasma-C5a with adult respiratory distress syndrome. *Lancet*, **1**, 947.

Haslam, P. L., Townsend, P. J., and Branthwaite, M. A. (1980). Complement activation during cardiopulmonary bypass. *Anaesthesia*, **35**, 22.

Heier, H. E., Kornstad, L., and Nordhagen, R. (1981). Differential coating of human red blood cells with C4 or C3 in a low ionic strength medium. *Vox. Sang.*, **41**, 249.

Hugli, T. E. (1979). Complement anaphylotoxins as plasma mediators, spasmogens and chemotoxins; in *Current Topics in Molecular Immunology* (eds R. A. Reisfeld and W. J. Mandy), p. 255. New York: Plenum Press.

Kirklin, J. W. (1980). Open heart surgery at the Mayo Clinic. The 25th anniversary. *Mayo Clin. Proc.*, **55**, 339.

Lachmann, P. J., and Hobart, M. H. (1978). Complement technology; in *Handbook of Experimental Immunology*, 3rd edn, Chapter 5a. (ed. D. M. Weir.) Blackwell: Oxford.

Loos, M., Volkanis, E., and Stroud, R. M. (1976). Mode of interaction of different polyanions with the first ($C_1$, $\overline{C1}$) the second ($C_2$) and the fourth ($C_4$) component of complement. II. *Immunochemistry*, **13**, 257.

Parker, D. J., Cantrell, J. W., Karp, R. B., Stroud, R. M., and Digerness, B. A. (1972). Changes in serum complement and immunoglobulins following cardiopulmonary bypass. *Surgery*, **71**, 824.

Perrin, L. H., Lambert, P. H., and Miescher, P. A. (1975). Complement breakdown products in plasma from patients with systemic lupus erythematosus and patients with membranoproliferative or other glomerulonephritis. *J. Clin. Invest.*, **56**, 165.

Pretty, H. M., Fudenberg, H. H., Perkins, H. A., and Gerbode, F. (1968). Anti γ-globulin antibodies after open heart surgery. *Blood*, **32**, 205.

Pruitt, K. M., Stroud, R. M., and Scott, J. W. (1971). Blood damage in the heart–lung machine. *Proc. Soc. Exp. Biol. Med.*, **137**, 714.

Raepple E., Hill, H., and Loos, M. (1976). Mode of interaction of different polyanions with the first ($C_1$, $\overline{C1}$), the second ($C_2$) and the fourth ($C_4$) component of complement. I. *Immunochemistry*, **13**, 251.

Ruddy, S., Carpenter, C. B., Chin, K. W., Knostman, J. N., Soter, N. A., Gotze, O., Muller-Eberhard, H. J., and Austen, K. F. (1976). Human complement metabolism: An analysis of 144 studies. *Medicine (Baltimore)*, **54**, 165.

Schifferli, J. A., Boralessa, H., Howarth, H. L., Whitwam, J. G., and Rees, A. J. (1982). Complement in CPD stored blood. *Vax. Sang.*, **42**, 198.

Szymanski, I. O., and Odgren, P. R. (1979). Studies on the preservation of red blood cells: attachment of the third component of human complement to erythrocytes during storage at 4 °C. *Vox. Sang.*, **36**, 213.

## MODIFICATIONS PERI-OPERATOIRES DU COMPLEMENT EN RAPPORT AVEC LA CIRCULATION EXTRACORPORELLE

### RESUME

Le complément hémolytique total ($CH_{50}$), les fractions C3 et C4 du complément, le produit de dégradation C3d du complément, la voie d'activation alterne et la transferrine, ont été mesurés avant, pendant et après circulation extracorporelle. Comme prévu, $CH_{50}$ diminuait après héparinisation, demeurait bas pendant la circulation extracorporelle et continuait à baisser jusqu'à 8 heures après la circulation extracorporelle. C3 et C4 diminuaient significativement pendant la CEC, continuaient à diminuer pendant encore 8 heures après la CEC (de 35% et 40% respectivement), puis remontaient ensuite progressivement pendant 48 h. Bien que les déplétions observées soient évocatrices d'une activation du complément, il n'y avait pas d'augmentation objectivable de C3d, et chez tous les patients la concentration de C3d restait dans les limites de la normale. Nous en concluons donc que des déplétions du complément de cette amplitude avaient peu de chance d'être dues à une activation du complément. Des modifications non spécifiques des concentrations protéiques au cours de la CEC, dues à la dilution, à la redistribution ou à d'autres facteurs non identifiés, sont des causes plus probables des diminutions observées. La réponse en phase aiguë à la chirurgie peut être un facteur expliquant l'augmentation secondaire de C3 et C4 constatée 24 heures après la CEC. Comme on sait que les concentrations de transferrine dans le plasma diminuent au cours de cette réponse, les diminutions observées des concentrations de transferrine corroborent cette notion.

## PERIOPERATIVE VERÄNDERUNGEN DES KOMPLEMENTES BEI KARDIOPULMUNALEM BYPASS

### ZUSAMMENFASSUNG

Das gesamte hämolytische Kompliment ($CH_{50}$), die Komplementkomponenten C3 und C4, das Komplement abbauprodukt C3d, die alternative pathway Aktivierung und Transferrin wurden vor, während und nach dem pulmonalem Bypass gemessen. Wie zu erwarten fiel $Ch_{50}$ nach der Heparinisierung, blieb niedrig während des Bypasses, und fiel bis 8 h nach dem Bypass weiter ab. C3 und C4 waren während dem Bypass signifikant erniedrigt, fielen bis 8 h nach dem Bypass weiter ab (35% und 40%) und stiegen danach 48 h lang allmählich an. Obwohl die Verarmung für eine Komplementaktivierung sprach, konnten keine C3d Anstiege gezeigt werden, und bei allen Patienten blieb die C3d Konzentration im normalen Bereich. Daraus wurde geschlossen, daß Komplement verarmungen dieser Grössenordnung wahrscheinlich nicht auf eine Komplementaktivierung zurückzuführen sind. Unspezifische Veränderungen der Proteinkonzentrationen währen dem Bypass, entweder durch Verdünnung hervorgerufen, Umverteilung oder andere noch unbekannte Faktoren, sind wahrscheinlichere Ursachen der beobachteten erniedrigten Werte. Die akute Reaktion auf die Operation mag ein Faktor des nachfolgenden Anstiegs von C3 und C4 sein, wie es 24 h nach dem Bypass zu beobachten ist. Da bekannt ist, daß de Transferrinkonzentrationen während dieser Reaktion abfallen, würde der beobachtete Abfall des Transferrins diese Ansicht unterstützen.

## CAMBIOS PERIOPERATORIOS DEL COMPLEMENTO ASOCIADOS CON DERIVACIÓN CARDIOPULMONAR

### SUMARIO

En el curso de derivaciones cardiopulmonares y después de las mismas, se procedió a la medición del complemento hemolítico total ($CH_{50}$), de los componentes del complemento C3 y C4, del producto de desintegración del complemento C3d, de la activación de la vía alterna así como de la transferrina. Tal como se esperaba, el $CH_{50}$ disminuyó después de la heparinización, se mantuvo bajo durante la derivación y se redujo aún más hasta 8 h. después de la derivación. Los C3 y C4 disminuyeron de manera significante durante la derivación, siguieron bajando durante 8 h. más después de la derivación (en un 35% y un 40% respectivamente) y luego aumentaron progresivamente durante las 48 h. siguientes. A pesar de las depleciones observados, lo que sugiere una activación del complemento, no hubo aumentos comprobables del C3d, y en todos los pacientes, la concentración del C3d se mantuvo dentro de los límites normales. Por lo tanto, se concluyó que las depleciones del complemento de tal magnitud, con poca probabilidad, podían resultar de la activación del complemento. Cambios no-específicos de las concentraciones de proteinas durante la derivación resultantes de la dilución, de la redistribución u otros factores no-identificados constituyen las causas más probables de las reducciones observadas. La respuesta aguda de fase a la cirujía puede ser un factor de los aumentos consecutivos del C3 y del C4 que se verifican 24 h. después de la derivación. Puesto que se sabe que las concentraciones de transferrina en el plasma bajan durante dicha respuesta, la disminución observada en la concentración de transferrina podría corroborar este punto de vista.

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# HAEMODYNAMIC RESPONSES TO INDUCTION OF ANAESTHESIA USING MIDAZOLAM IN CARDIAC SURGICAL PATIENTS

U. SCHULTE-SASSE, W. HESS and J. TARNOW

## SUMMARY

The cardiovascular effects of midazolam 0.2 mg $kg^{-1}$ i.v. were studied during the induction of anaesthesia in 16 premedicated patients subjected to cardiac surgery. In eight patients with coronary artery disease in whom global resting left ventricular function was normal the haemodynamic changes were small and observations on arterial pressure, cardiac index, stroke index, cardiac filling pressures, systemic and pulmonary vascular resistance appeared to parallel those accompanying deep sleep in healthy volunteers. In eight patients with valvular heart disease and haemodynamic evidence of moderately impaired cardiac performance, pump function during induction with midazolam was maintained, probably as a result of the tendency towards a decrease in systemic vascular resistance. Midazolam appears to be a valuable alternative to conventional induction agents without adverse effects on the cardiovascular system.

The benzodiazepines are recommended frequently for the induction of anaesthesia in cardiac surgical patients. Diazepam is used widely for this purpose and has become popular because of the profound amnesia produced and its relatively minor effects on the cardiovascular system (Côté, Gueret and Bourassa, 1974; Stanley et al., 1976; Clarke and Lyons, 1977; Jones, Stehling and Zauder, 1979; Tarnow et al., 1979; McCammon, Hilgenberg and Stoelting, 1980). In addition, a coronary vasodilator effect of diazepam has been suggested (Ikram, Rubin and Jewkes, 1973) and there is evidence that, in patients with increased left ventricular filling pressures, a small dose of diazepam can decrease this pressure (Côté, Campeau and Bourassa, 1976). A major disadvantage of diazepam is its insolubility in water, and the organic solvents used to make the drug soluble may cause pain on injection with subsequent thrombophlebitis (Langdon, Harlan and Bailey, 1973). The new compound midazolam appears to share the beneficial characteristics of other benzodiazepines. However, it is unique in that it is water soluble.

Haemodynamic responses to the administration of midazolam have been studied in healthy volunteers (Brown et al., 1979; Forster et al., 1980), in non-cardiac surgical patients without heart disease (Conner et al., 1978; Fragen, Gahl and Caldwell, 1978; Reves, Corssen and Holcomb, 1978; Reves et al., 1979; Larsen et al., 1981) and in patients with coronary artery disease (Fragen et al., 1979; Reves, Samuelson and Lewis, 1979; Samuelson et al., 1981), and have demonstrated only minimal alterations in cardiovascular function.

We investigated the circulatory effects of midazolam during the induction of anaesthesia in patients with impaired ventricular function who were about to undergo replacement of the aortic or mitral valve, or both. The results were compared with the haemodynamic effects of midazolam in patients with coronary artery disease and normal resting left ventricular function.

## PATIENTS AND METHODS

Sixteen cardiac surgical patients were studied. Written informed consent was obtained at the time of the preoperative visit. One group consisted of eight patients (age 39–68 yr, mean 53 yr) with normal resting left ventricular function ($PCWP < 12$ mm Hg, ejection fraction ($EF) > 0.5$ at the time of diagnostic catheterization) about to undergo coronary bypass surgery. A second group of eight patients (age 43–75 yr, mean 60 yr) with valvular heart disease (four with aortic stenosis, one with aortic regurgitation and three with mitral valve stenosis) and increased left ventricular filling pressures ($PCWP > 19$ mm Hg) and reduced ejection fractions ($< 0.5$) during diagnostic catheterization. The patients with mitral valve stenosis were in atrial

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fibrillation. In the patients with coronary artery disease (CAD) maintenance antianginal therapy consisted of nitroglycerine or long-acting nitrates (isosorbide dinitrate 60–120 mg day$^{-1}$) and propranolol 40–240 mg day$^{-1}$ by mouth. Five patients of the CAD-group and all of the patients with valvular heart disease (VHD) received digitalis. The daily maintenance dose of glycosides was $\beta$-acetyldigoxin 0.2–0.4 mg. The last single dose of these drugs was given 12–16 h before operation.

All patients were premedicated with flunitrazepam 2 mg by mouth 90 min before the induction of anaesthesia. Upon arrival in the operating theatre, electrocardiogram leads were attached, a peripheral i.v. cannula and a 20-gauge radial artery catheter were placed. A 7-F thermodilution flow-directed catheter was introduced to the pulmonary circulation via the right jugular vein. This catheter was used for measuring right atrial pressure (RAP), pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP). All pressures were measured using Statham P 23 transducers and were recorded together with a lead $V_5$ of the electrocardiogram on a Hellige EK 21 eight-channel recorder and display oscilloscope. Cardiac output (CO) was determined in duplicate (control, 7th and 20th min) utilizing the thermodilution method (Edwards 9620 cardiac output computer). The temperature curve was monitored on an Edwards 9812 recorder. Values of CO were accepted if within ±0.2 litre min$^{-1}$; if results deviated from these limits, a third determination was obtained. Duplicate measurements at the 1st, 3rd and 5th min were prohibited by the design of the study. Systemic and pulmonary vascular resistance (SVR, PVR), cardiac index (CI) and stroke index (SI) were calculated. The heart rate–systolic arterial pressure product (RPP) was used as an index of myocardial oxygen demand.

The patients were allowed to rest for about 15 min after the cannulation procedure before a series of control measurements was taken. Midazolam 0.2 mg kg$^{-1}$ was injected into a peripheral vein within 15 s. Measurements at 2-min intervals were made over a period of 7 min during which ventilation was assisted (100% oxygen) to maintain end-tidal carbon dioxide 5% (Datex $CO_2$-analyser 101). Then fentanyl (5 $\mu$g kg$^{-1}$ in VHD-patients; 7.5 $\mu$g kg$^{-1}$ in CAD patients) and pancuronium bromide 0.1 mg kg$^{-1}$ were administered and the trachea intubated. Further measurements were made immediately (within 30 s) following tracheal intubation and 20 min after the injection of midazolam under conditions of controlled normoventilation (50% nitrous oxide in oxygen) using an Engstrom ventilator (ER 300).

Statistical analyses were performed using the paired Wilcoxon test for comparison of haemodynamic data within the same subjects. The maximum changes following the administration of midazolam (usually observed between the 3rd and the 5th min) and the data obtained at the end of the observation period were compared with the control values in the awake patients.

To analyse the haemodynamic effects of laryngoscopy and tracheal intubation, the variables obtained immediately following intubation were compared with the preintubation values observed at the 7th min. Statistical significance was defined as $2\alpha < 0.05$. Data are presented as means ± SEM.

## RESULTS

The induction of anaesthesia using midazolam 0.2 mg kg$^{-1}$ was associated with a decrease in mean arterial pressure (m.a.p.) from 92 mm Hg to 80 mm Hg 5 min after injection in the CAD-group (fig. 1). Similar small changes were observed in the patients with valvular heart disease. There was no arterial pressure response to the stimulus of laryngoscopy and intubation after the addition of fentanyl. At the end of the observation period m.a.p. in both groups was significantly less than in the awake patients.

Midazolam significantly decreased cardiac index in the CAD-group. In the patients with valvular heart disease CI tended to increase, but the observed changes did not reach the level of statistical significance. Following the administration of fentanyl, cardiac index was found to be significantly decreased after 20 min in the CAD-group (compared with the control values in the awake patients).

Heart rate did not change during the entire observation period (fig. 2). In the patients with sinus rhythm no arrhythmias were observed, and new e.c.g. changes indicative of ischaemia did not occur.

Midazolam did not influence stroke index in the patients with VHD; the decrease of the SI observed in the CAD-group reflected the changes in the cardiac index.

Midazolam alone exerted no major effects on mean pulmonary artery pressure or on left and right ventricular filling pressure (fig. 3). These values increased slightly following laryngoscopy and intubation. Under steady-state conditions (20 min after

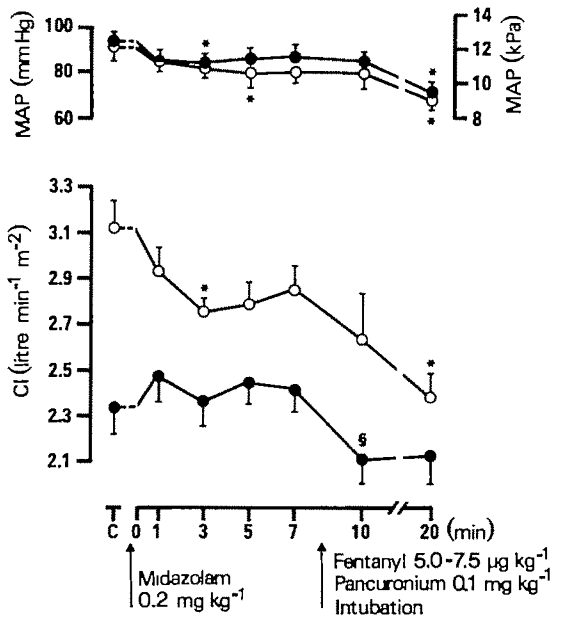

FIG. 1. Changes in mean arterial pressure and cardiac index (mean ± SEM) during induction of anaesthesia with midazolam and fentanyl in patients with coronary artery disease (○; $n = 8$) and in patients with valvular heart disease (●; $n = 8$). C = controls (awake patients); *$2\alpha < 0.05$ (compared with control value); §$2\alpha < 0.05$ (post-intubation value compared with the pre-intubation value obtained at the 7th min.

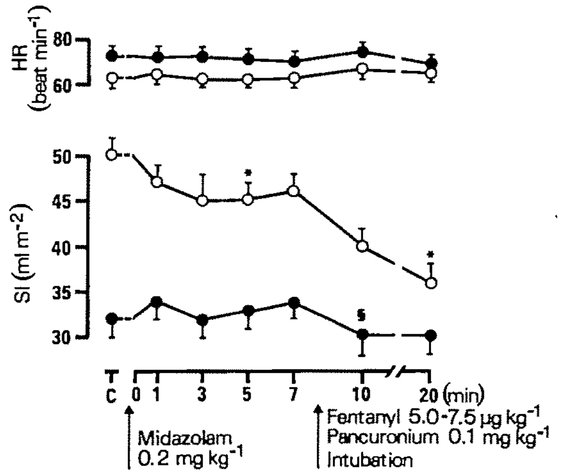

FIG. 2. Changes in heart rate and stroke index (mean ± SEM) during induction of anaesthesia with midazolam and fentanyl in patients with coronary artery disease (○; $n = 8$) and in patients with valvular heart disease (●; $n = 8$). For abbreviations and symbols, see figure 1.

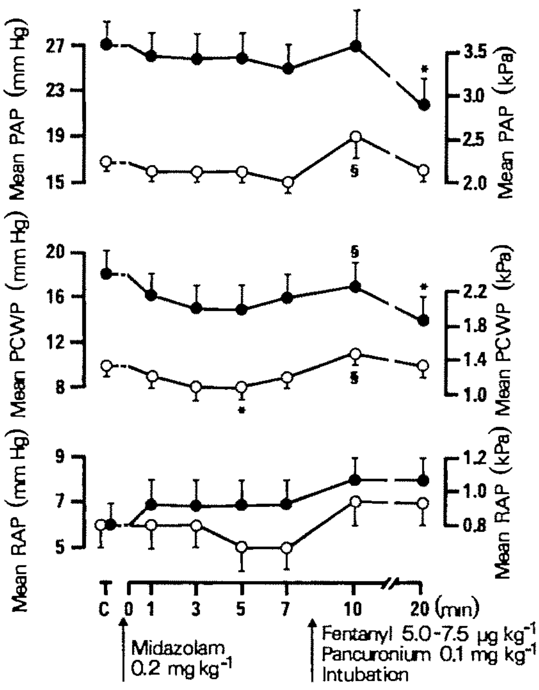

FIG. 3. Changes in mean pulmonary artery pressure, mean pulmonary capillary wedge pressure and mean right atrial pressure (mean ± SEM) during induction of anaesthesia with midazolam and fentanyl in patients with coronary artery disease (○; $n = 8$) and in patients with valvular heart disease (●; $n = 8$). For abbreviations and symbols see figure 1.

induction of anaesthesia) mean PAP and mean PCWP in the VHD-group were decreased significantly when compared with control values.

Systemic vascular resistance remained largely unaffected (fig. 4). In the VHD-patients the increased control values tended to decrease after midazolam. At the end of the observation period (after the addition of fentanyl) SVR in this group was significantly less than in the awake patients. There were no major changes in the pulmonary vascular resistance during the induction of anaesthesia with midazolam and fentanyl.

The heart rate–systolic arterial pressure product (fig. 5), an indirect index of myocardial oxygen consumption, changed only little with midazolam or midazolam and fentanyl.

The onset of sleep, as measured by the loss of the eyelash reflex or lack of response to oral command, occurred within 2 min in 13 of 16 patients. Three patients lost consciousness only after the addition of fentanyl. No patient complained of pain during the injection of midazolam.

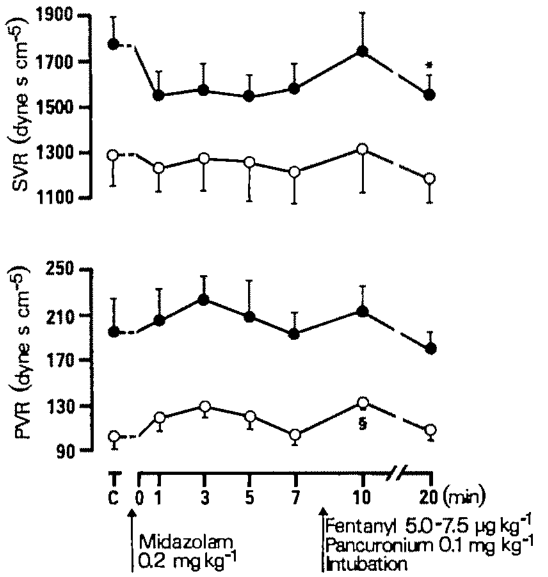

FIG. 4. Changes in systemic and pulmonary vascular resistance (mean ± SEM) during induction of anaesthesia with midazolam and fentanyl in patients with coronary artery disease (○; $n = 8$) and in patients with valvular heart disease (●; $n = 8$). For abbreviations and symbols, see figure 1.

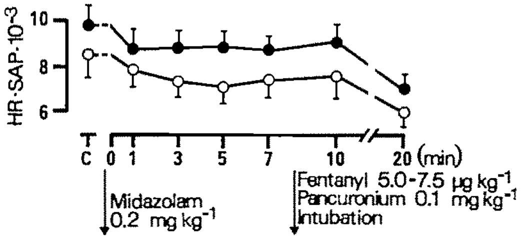

FIG. 5. Changes in the heart rate–systolic arterial pressure product (mean ± SEM) during induction of anaesthesia with midazolam and fentanyl in patients with coronary artery disease (○; $n = 8$) and in patients with valvular heart disease (●; $n = 8$).

## DISCUSSION

The benzodiazepines have an established place in anaesthetic practice as sedative hypnotics and some have been used as i.v. induction agents.

In cardiac surgical patients diazepam or flunitrazepam are commonly used as induction agents because of their minimal effects on the cardiovascular system (Coleman et al., 1973; Côté, Guéret and Bourassa, 1974; Stanley et al., 1976; Clarke and Lyons, 1977; Tarnow et al., 1979; McCammon, Hilgenberg and Stoelting, 1980). We have investigated the new water-soluble benzodiazepine derivative midazolam. Despite some statistically significant haemodynamic variations, our findings in patients with CAD, in whom global resting left ventricular function was normal, indicate that midazolam can be safely used as an induction agent. The haemodynamic changes are modest and observations on arterial pressure, cardiac output, stroke volume and systemic vascular resistance parallel those accompanying deep sleep in normal volunteers (Khatri and Freis, 1967). The data of Samuelson and colleagues (1981) showed that midazolam does not blunt the haemodynamic response to intubation. The lack of cardiovascular changes during laryngoscopy and intubation in our patients is probably a result of mainly the addition of fentanyl, and thus prevented an increase in myocardial oxygen demand. The lack of response to this stimulus may also reflect a fair degree of beta-adrenergic blockade in CAD-patients receiving propranolol before operation. Our results largely confirm the findings of others, who studied the effects of low doses of midazolam ($0.05\,mg\,kg^{-1}$ i.v.) used as sedative in patients undergoing diagnostic cardiac catheterization (Fragen et al., 1979) or who administered midazolam $0.2\,mg\,kg^{-1}$ for the induction of anaesthesia in patients undergoing myocardial revascularization (Samuelson et al., 1981).

In contrast to our findings, Samuelson and coworkers (1981) reported a significant decrease in pulmonary artery and capillary wedge pressures 5 min after the administration of midazolam, which was probably a result of the fact that control values in their patients were in the upper normal range (22 mm Hg and 16 mm Hg respectively).

Reves, Samuelson and Lewis (1979) studied the effect of midazolam $0.2\,mg\,kg^{-1}$ in a group of five CAD-patients with low cardiac output, high left ventricular filling pressure and increased systemic vascular resistance. Under these conditions midazolam produced a substantial decrease in systemic vascular resistance, thereby allowing a significant improvement in pump function and a decrease in the increased left ventricular filling pressure. The differences between these findings and our results in CAD-patients are probably related to conditions of vascular tone present before the injection of the drug.

As far as we know, midazolam has not previously been investigated in patients with valvular heart disease. In this study, following the administration of midazolam to a group of VHD-patients with haemodynamic evidence of moderately decreased cardiac performance, pump function was maintained probably as a result of the tendency towards a decrease in systemic vascular resistance.

In conclusion, the significance of these observations and those reported by Reves, Samuelson and Lewis (1979) is the demonstration of the safety and, perhaps, potentially beneficial effect of midazolam in patients with an increase in systemic vascular resistance secondary to heart disease in whom myocardial performance is maintained or may even improve with a decrease of afterload. Although midazolam does not dethrone other induction agents, it certainly is a useful hypnotic with definite advantages.

## REFERENCES

Brown, C. R., Sarnquist, F. H., Canup, C. A., and Pedley, T. A. (1979). Clinical, electroencephalographic, and pharmacokinetic studies of a water-soluble benzodiazepine, midazolam maleate. *Anesthesiology*, **50**, 467.

Clarke, R. S. J., and Lyons, S. M. (1977). Diazepam and flunitrazepam as induction agents for cardiac surgical operations. *Acta Anaesthesiol. Scand.*, **21**, 282.

Coleman, A. J., Downing, J. W., Moyes, D. G., and O'Brien, A. (1973). Acute cardiovascular effects of Ro 5-4200: A new anaesthesia induction agent. *S. Afr. Med. J.*, **47**, 382.

Conner, J. T., Katz, R. L., Pagano, R. R., and Graham, C. W. (1978). Ro 21-3981 for intravenous surgical premedication and induction of anesthesia. *Anesth. Analg. (Cleve.)*, **57**, 1.

Côté, P., Campeau, L., and Bourassa, M. G. (1976). Therapeutic implications of diazepam in patients with elevated left ventricular filling pressure. *Am. Heart J.*, **91**, 747.

——Guéret, P., and Bourassa, M. G. (1974). Systemic and coronary hemodynamic effects of diazepam in patients with normal and diseased coronary arteries. *Circulation*, **50**, 1210.

Forster, A., Gardaz, J.-P., Suter, P. M., and Gemperle, M. (1980). I.v. midazolam as an induction agent for anaesthesia: a study in volunteers. *Br. J. Anaesth.*, **52**, 907.

Fragen, R. J., Gahl, F., and Caldwell, N. (1978). A water-soluble benzodiazepine, Ro 21-3981, for induction of anesthesia. *Anesthesiology*, **49**, 41.

——Meyers, S. N., Barresi, V., and Caldwell, N. J. (1979). Hemodynamic effects of midazolam in cardiac patients. *Anesthesiology*, **51**, S103.

Ikram H., Rubin, A. P., and Jewkes, R. F. (1973). Effect of diazepam on myocardial blood flow of patients with and without coronary artery disease. *Br. Heart J.*, **35**, 626.

Jones, D. J., Stehling, L. C., and Zauder, H. L. (1979). Cardiovascular responses to diazepam and midazolam maleate in the dog. *Anesthesiology*, **51**, 430.

Khatri, I.M., and Freis, E. D. (1967). Hemodynamic changes during sleep, *J. Appl. Physiol.*, **22**, 867.

Langdon, D. E., Harlan, J. R., and Bailey, R. L. (1973). Thrombophlebitis with diazepam used intravenously. *J.A.M.A.*, **223**, 184.

Larsen, R., Hilfiker, O., Radke, J., and Sonntag, H. (1981). The effects of midazolam on the general circulation, cerebral bloodflow and cerebral oxygen consumption in man. *Anaesthesist*, **30**, 18.

McCammon, R. L., Hilgenberg, J. C., and Stoelting, R. K. (1980). Hemodynamic effects of diazepam and diazepam–nitrous oxide in patients with coronary artery disease. *Anesth. Analg. (Cleve.)*, **59**, 438.

Reves, J. G., Corssen, G., and Holcomb, C. (1978). Comparison of two benzodiazepines for anaesthesia induction: midazolam and diazepam. *Can. Anaesth. Soc. J.*, **25**, 211.

——Samuelson, P. N., and Lewis, S. (1979). Midazolam maleate induction in patients with ischaemic heart disease: haemodynamic observations. *Can. Anaesth. Soc. J.*, **26**, 402.

——Vinik, R., Hirschfield, A. M., Holcomb, C., and Strong, S. (1979). Midazolam compared with thiopentone as a hypnotic component in balanced anaesthesia: a randomized, double-blind study. *Can. Anaesth. Soc. J.*, **26**, 42.

Samuelson, P. N., Reves, J. G., Kouchoukos, N. T., Smith, L. R., and Dole, K. M. (1981). Hemodynamic responses to anesthetic induction with midazolam or diazepam in patients with ischemic heart disease. *Anesth. Analg. (Cleve.)*, **60**, 802.

Stanley, T. H., Bennett, G. M., Loeser, E. A., Kawamura, R., and Sentker, C. R. (1976). Cardiovascular effects of diazepam and droperidol during morphine anesthesia. *Anesthesiology*, **44**, 255.

Tarnow, J., Heß, W., Schmidt, D., and Eberlein H. J. (1979). Induction of anaesthesia in patients with coronary artery disease: flunitrazepam, diazepam, ketamine, fentanyl. A haemodynamic study. *Anaesthesist*, **28**, 9.

## REPONSES HEMODYNAMIQUES A L'INDUCTION DE L'ANESTHESIE PAR LE MIDAZOLAM CHEZ DES PATIENTS DE CHIRURGIE CARDIAQUE

### RESUME

Les effets cardiovasculaires du midazolam 0,2 mg kg$^{-1}$ i.v. ont été étudiés lors de l'induction de l'anesthéaie chez 16 paitents prémédiqués, candidats à la chirurgie cardiaque. Chez huit patients coronariens, dont la fonction ventriculaire gauche globale au repos était normale, les modifications hémodynamiques sont restées discrètes et les variations de pression artérielle, d'index cardiaque, d'index systolique, de pressions de remplissage et de résistances artérielles systémiques et pulmonaires étaient comparables à celles observées au cours du sommeil profond chez des volontaires sains. Chez huit patients porteurs de valvulopathies et ayant des signes hémodynamiques d'atteinte modérée de la fonction cardiaque, la fonction de la pompe a été maintenue au cours de l'induction par le midazolam, probablement du fait de la tendance à la baisse des résistances vasculaires systémiques. Le midazolam semble représenter une alternative intéressante aux agents d'induction conventionnels sans effets néfastes sur le système cardio-vasculaire.

# DIE HÄMODYNAMISCHE REAKTION AUF DIE NARKOSEEINLEITUNG MIT MIDAZOLAM BEI PATIENTEN IN DER HERZCHIRURGIE

## ZUSAMMENFASSUNG

Es wurden die kardiovaskulären Auswirkungen von Midazolam 0,2 mg kg$^{-1}$ bei der Narkoseeinleitung an 16 prämedizierten Patienten studiert, die sich einer Herzoperation unterziehen mußten. Bei acht Patienten mit koronarer Herzkrankheit, bei denen die globale Leistung des linken Ventrikels in-Ruhe normal war, blieben die hämodynamischen Veränderungen klein und die Beobachtung von arteriellem Druck, Herzindex, Schlagindex, den kardialen Füllungsdrucken, des systemischen und pulmonalen Gefäßwiederstandes schien gleichzulaufen mit den bei gesunden freiwilligen Versuchspersonen in tiefem Schlaf zu beobachtenden Werten. Bei acht Patienten mit Herzklappenfehlern und hämodynamisch wirksam mäßig verschlechterter Herzleistung, blieb die Pumpenfunktion während der Einleitung mit Midazolam aufrechterhalten, was wahrscheinlich auf die Tendenz zu einem Abfall des vaskulären Gefäßwiederstandes zurückzuführen ist. Midazolam scheint eine wirkliche Alternative zu herkömmlichen Einleitungsmitteln ohne umgekehrte Auswirkung auf das kardiovaskuläre System zu sein.

# RESPUESTAS HEMODINÁMICAS A LA INDUCCIÓN DE ANESTESIA POR MIDAZOLAM EN PACIENTES SOMETIDOS A CIRUJÍA CARDÍACA

## SUMARIO

Se estudiaron los efectos cardio-vasculares del midazolam en dosis de 0,2 mg/kg$^{-1}$ i.v. durante la inducción de anestesia en 16 pacientes con premedicación sometidos a cirujía cardíaca. En 8 de los pacientes que padecían de enfermedad de la arteria coronaria y en los que la función ventricular izquierda de reposo global era normal, los cambios hemodinámicos fueron muy pequeños y las observaciones concernientes a la presión arterial, el índice cardíaco, el índice sistólico, las presiones de relleno cardíaco, la resistancia sistémica y vascular pulmonar parecían estar en paralelo con los que acompañan el sueño profundo en voluntarios sanos. En ocho de los pacientes que sufrían de enfermedad cardíaca valvular y mostraban una señal hemodinámica de rendimiento cardíaco moderadamente deteriorado, se mantuvo la función de bombeo durante la inducción por Midazolam, probablemente como resultado de la tendencia hacia una disminución de la resistancia vascular sistémica. El midazolam parece ser una solución alternativa de los agentes de inducción tradicionales sin efectos adversos sobre el sistema cardiovascular.

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# I.M. OR I.V. ATROPINE OR GLYCOPYRROLATE FOR THE PREVENTION OF OCULOCARDIAC REFLEX IN CHILDREN UNDERGOING SQUINT SURGERY

R. K. MIRAKHUR, C. J. JONES, J. W. DUNDEE AND D. B. ARCHER

## SUMMARY

The frequency and nature of the oculocardiac reflex and its prevention by atropine or glycopyrrolate (i.m. and i.v.) have been studied in 160 children undergoing surgery for the correction of squint. Ninety per cent of those given no anticholinergic premedication exhibited the reflex. This was decreased to about 50% in those receiving the drugs i.m. Glycopyrrolate 7.5 $\mu g\,kg^{-1}$ and atropine 15 $\mu g\,kg^{-1}$ i.v. were effective in most instances, the latter being slightly better. However, glycopyrrolate was associated with tachycardia of smaller magnitude. The reflex was observed more often following traction on the medial rectus muscle.

Decreases in heart rate or arrhythmia, or both, are common during surgery on the extraocular muscles (Bosomworth, Ziegler and Jacoby, 1958; Moonie, Ress and Elton, 1964; Alexander, 1975). The frequency may be as high as 90% in patients not receiving atropine although even following the administration of atropine i.m. Alexander (1975) found it to be 70%. The administration of atropine i.v. decreased the frequency to 25% with only minimal decreases in heart rate. However, this may be associated *per se* with arrhythmia (Mendelblatt, Kirsch and Lemberg, 1962; Pontinen, 1966; Schwartz, 1971).

Premedication with glycopyrrolate i.m. has been associated with a lower frequency of arrhythmia during the induction of anaesthesia in adult patients (Mirakhur et al., 1978). However, the efficacy of this anticholinergic drug in the prevention of the oculocardiac reflex does not appear to have been evaluated following i.m. administration. This has been examined in the present study and compared with the efficacy of atropine. In addition, the efficacy of the two drugs was compared following i.v. administration, since this method is considered more effective (Alexander, 1975; Dewar and Wishart, 1976). A group receiving placebo (i.v.) was included for comparison.

## PATIENTS AND METHODS

Children, between the ages of 1 and 14 yr and weighing between 9 and 47 kg (ASA Grade I), undergoing corrective surgery for squint, were studied. None was receiving any concurrent medication. The study was approved by the Regional Ethics Committee. All were premedicated with pethidine 1.0 $mg\,kg^{-1}$ administered i.m. about 1 h before the induction of anaesthesia.

One hundred and sixty patients were studied and were divided into eight groups of 20 patients each (Groups I–VIII). The doses and routes of administration of the anticholinergic drugs are shown in table I, with the mean ages and weights of the patients. Those receiving the drugs i.m. received these with the pethidine. The drugs administered i.v. were given 5 min before the induction of anaesthesia (i.v. induction) or as soon as a vein could be cannulated following inhalation induction.

The anticholinergic drugs were administered randomly from specially prepared coded ampoules.

Anaesthesia was induced with thiopentone 4–6 $mg\,kg^{-1}$ or halothane in a mixture of nitrous oxide and oxygen. Suxamethonium 1.0 $mg\,kg^{-1}$ was given i.v., the larynx sprayed with 4% lignocaine and the trachea intubated. Anaesthesia was maintained with nitrous oxide and halothane in oxygen. Respiration was spontaneous.

The electrocardiogram (e.c.g.) was monitored from the start of induction to the end of surgery. E.c.g. changes were recorded during the induction of anaesthesia, when the surgeon was applying traction to the extraocular muscles and at intervals during the surgical procedure.

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TABLE I. *Doses, routes of administration of the two drugs and physical characteristics of the patients*

| Group No. | Drugs | Dose ($\mu g\ kg^{-1}$) | Route | Mean age (yr ± SEM) | Mean weight (kg ± SEM) |
|---|---|---|---|---|---|
| I | Atropine | 15 | i.m. | 6.7±0.6 | 23.2±1.7 |
| II | Glycopyrrolate | 5 | i.m. | 6.5±0.8 | 22.7±1.7 |
| III | Glycopyrrolate | 10 | i.m. | 5.5±0.5 | 20.4±1.4 |
| IV | Atropine | 10 | i.v. | 7.6±0.8 | 25.8±2.0 |
| V | Atropine | 15 | i.v. | 8.3±0.6 | 26.0±1.7 |
| VI | Glycopyrrolate | 5 | i.v. | 7.2±0.8 | 24.3±1.9 |
| VII | Glycopyrrolate | 7.5 | i.v. | 7.1±0.5 | 21.1±1.1 |
| VIII | Placebo | — | i.v. | 7.7±0.5 | 25.6±1.4 |

Bradycardia, defined as a heart rate of 70 beat $min^{-1}$ or less occurring at any time during surgery and persisting for more than 15 s, was treated with an additional increment of glycopyrrolate or atropine (after breaking the code) or by requesting the surgeon to release the tension on the muscle, or both. The oculocardiac reflex was defined as slowing of the heart rate by more than 20%, or the occurrence of an arrhythmia during traction, irrespective of the heart rate.

The heart rates within the groups and between the groups were subjected to a paired and non-paired *t* test respectively, to determine statistical significance. The statistical significance of the frequency of the presence of a reflex response or arrhythmia was tested with Fisher's exact test.

## RESULTS

Anaesthesia was induced i.v. in 135 children, an inhalation induction being used in the remainder.

Basal heart rates and heart rate 1 h after the administration of both drugs i.m. are shown in table II. Glycopyrrolate 5 $\mu g\ kg^{-1}$ produced a small and insignificant increase in heart rate, whereas atropine and the larger dose of glycopyrrolate increased the heart rate significantly, by approximately 30%. The heart rates in the groups receiving the drugs i.v. are given in table III. Apart from the group receiving the placebo, there were significant increases in heart rate at 5 min in all the other groups.

TABLE II. *Heart rates (± SEM) in children receiving premedication i.m. (pethidine + atropine or glycopyrrolate).* *$P < 0.001$ *compared with basal heart rate. For identification of the goups see table I*

| Group | Basal heart rate (beat $min^{-1}$) | Heart rate 1 h after pre-med (beat $min^{-1}$) |
|---|---|---|
| I | 98±3.5 | 127±4.3* |
| II | 103±3.1 | 113±4.2 |
| III | 106±2.4 | 136±5.0* |

The frequency and nature of the oculocardiac reflex is given in table IV. While both atropine

TABLE III. *Heart rates (± SEM) in children receiving the anticholinergic drugs i.v.* *$P < 0.001$ *compared with heart rate before administration of drug. For identification of the groups see table I*

| Group | Heart rate before drug (beat $min^{-1}$) | Heart rate 5 min after drug (beat $min^{-1}$) |
|---|---|---|
| IV | 105±4.4 | 127±4.8* |
| V | 95±4.1 | 131±4.7* |
| VI | 93±3.6 | 112±4.3* |
| VII | 99±5.3 | 124±5.2* |
| VIII | 97±3.7 | 94±3.4 |

TABLE IV. *Frequency and nature of the oculocardiac reflex (OCR) (total no. of patients; percentage in parentheses). Some patients exhibited both bradycardia and arrhythmia. For identification of the groups see table I*

| Group | Total with OCR (%) | Decrease in heart rate >20% (%) | Arrhythmia during traction (%) |
|---|---|---|---|
| I | 10 (50) | 8 (40) | 5 (25) |
| II | 12 (60) | 9 (45) | 9 (45) |
| III | 8 (40) | 5 (25) | 4 (20) |
| IV | 5 (25) | 4 (20) | 2 (10) |
| V | 1 ( 5) | 0 | 1 ( 5) |
| VI | 5 (25) | 2 (10) | 4 (20) |
| VII | 3 (15) | 1 ( 5) | 3 (15) |
| VIII | 18 (90) | 16 (80) | 14 (70) |
| Total No. | 62 | 45 | 42 |

$15\,\mu g\,kg^{-1}$ and glycopyrrolate $10\,\mu g\,kg^{-1}$ i.m. produced significant tachycardia (table II), these, and glycopyrrolate $5\,\mu g\,kg^{-1}$, proved ineffective in nearly half the patients. On i.v. administration before surgery, both drugs proved effective in the majority of patients, particularly when the higher doses were used. There was no significant difference between the corresponding doses of atropine and glycopyrrolate. Not unexpectedly, the administration of saline was associated with the presence of the oculocardiac reflex in 90% of the patients ($P < 0.05-0.001$) when compared with all the other groups, except that given glycopyrrolate $5\,\mu g\,kg^{-1}$. Some patients exhibited both bradycardia and arrhythmia.

The number of patients undergoing surgery for convergent or divergent squints is shown in table V, which summarizes data from all the groups. This table is designed to illustrate the difference in the susceptibility of the different extraocular muscles to stretching, but not the effectiveness of any prophylaxis. In our hospital all patients with convergent squints have the medial rectus muscle recessed first, while those with divergent squints have surgery on the lateral rectus muscle first. The occurrence of the oculocardiac reflex was related to the muscle first tackled by the surgeon (table V). It is seen that the majority of the patients had operations for convergent squints and in 40% (58 of 144) of these the oculocardiac reflex was stimulated on stretching the medial rectus muscle, whereas 19% (three of 16) of those undergoing surgery for divergent squint showed the presence of the oculocardiac reflex on stretching the first muscle recessed (lateral rectus). Another pointer towards the greater sensitivity of the medial rectus is the fact that the reflex was present in one out of three patients (33%) in the divergent group on stretching the second muscle (medial rectus) whereas it was present on stretching the second muscle (lateral rectus) in only seven out of 58 patients (12%) in the convergent group.

The nature of the arrhythmias observed during traction on the extraocular muscles is shown in table VI. It is apparent that junctional rhythm and sinus arrest with nodal escape were the commonest arrhythmias, followed by the occurrence of ventricular ectopic beats.

Six patients received additional anticholinergic drug because of decreases in heart rate to less than 70 beat $min^{-1}$ and five of these were in the group receiving placebo. Two developed persistent ventricular ectopic beats of multifocal origin on the administration of atropine and were given lignocaine.

TABLE V. *Frequency of oculocardiac reflex in relation to type of squint. MR = Medial rectus; LR = lateral rectus*

| | Convergent squints ($n = 144$) | | Divergent squints ($n = 16$) | |
|---|---|---|---|---|
| | OCR on traction of | | OCR on traction of | |
| Total no. patients | 1st muscle (MR) | 2nd muscle (LR) | 1st muscle (LR) | 2nd muscle (MR) |
| 160 | 58 | 7 | 3 | 1 |

*TABLE VI. Number of patients showing the various types of arrhythmia during traction on the extraocular muscles (some patients exhibited more than one type of arrhythmia). NR = Nodal rhythm; JR = junctional rhythm. For identification of the groups see table I*

| Group | NR/JR including sinus arrest with a nodal escape rhythm | Ventricular ectopic beats including bigeminy | Other |
|---|---|---|---|
| I | 3 | 3 | |
| II | 8 | 2 | |
| III | 4 | — | 1 |
| IV | 2 | 1 | |
| V | 1 | — | |
| VI | 3 | 1 | 1 |
| VII | 1 | 2 | |
| VIII | 14 | — | 1 |

## DISCUSSION

That the heart rate decreases in response to traction on the extraocular muscles is evident from the present study. The overall frequency was approximately 40% (62 of 160 patients), but was 90% in those patients who did not receive anticholinergic drugs. The administration of anticholinergic drugs, even by the i.m. route, decreased the frequency, glycopyrrolate 10 $\mu g\,kg^{-1}$ being the most efficacious by this route. The frequency observed in the present study was lower than that reported by Katz and Bigger (1970) and Alexander (1975) who defined any slowing in heart rate or arrhythmias, or both, as evidence of a reflex response. We decided on a more practical aspect; a 20% decrease in heart rate or the presence of arrhythmias, or both, during traction indicated the presence of the reflex, since smaller decreases in heart rate do not usually require treatment.

Alexander (1975) pointed out that it was traction on the first muscle handled by the surgeon (which happened to be the lateral rectus in most of his patients) which gave rise to the changes in heart rate. We noticed that the oculocardiac reflex was present more frequently while traction was being applied to the medial rectus muscle, which was the first muscle operated on in most patients in our study. However, table V shows that it was the medial rectus muscle rather than the first muscle to be operated on that is of relevance, since only three of 16 patients having surgery to lateral rectus first exhibited presence of the reflex in contrast to 58 of 144 showing presence of the reflex on traction of the medial rectus first. These findings are in keeping with those of Bosomworth, Ziegler and Jacoby (1958), Mendelblatt, Kirsch and Lemberg (1962) and Apt, Isenberg and Gaffney (1973).

Various methods have been suggested to prevent stimulation of the oculocardiac reflex. Retrobulbar block with a local anaesthetic drug (Planten, 1963), the use of gallamine (Deacock and Oxer, 1962) or artificial ventilation (Aserinsky and Debias, 1963; Gandevia, McCloskey and Potter, 1978) have been tried. However, retrobulbar block is thought to be ineffective (Bosomworth, Ziegler and Jacoby, 1958) and has complications of its own (Berler, 1963; Katz and Katz, 1978). Although Katz and Katz (1978) advise no prophylaxis except careful monitoring and frequent inflation of the lung during the manipulations on the eye, the mainstay of prevention, and of treatment, is the administration of anticholinergic drugs like atropine (Alexander, 1975; Dewar and Wishart, 1976; Meyers and Tomeldan, 1979).

Whilst atropine, particularly i.v., does decrease the frequency of occurrence of the reflex responses (Alexander, 1975) it is believed by some that atropine itself may produce cardiac arrhythmia (Mendelblatt, Kirsch and Lemberg, 1962; Pontinen, 1966; Schwartz, 1971; Katz and Katz, 1978; Kwik, 1980). Glycopyrrolate has been suggested as an alternative (Meyers and Tomeldan, 1979), although these authors did not notice any difference in the efficacy of the two drugs.

The present study shows the greater effectiveness of the i.v. route of administration with both atropine and glycopyrrolate. There are no significant differences in the frequency of occurrence of the oculocardiac reflex at comparable doses of the two drugs (atropine 10 $\mu g\,kg^{-1}$ and glycopyrrolate 5 $\mu g\,kg^{-1}$ and 15 $\mu g\,kg^{-1}$ and 7.5 $\mu g\,kg^{-1}$ of atropine and glycopyrrolate respectively).

The occurrence of arrhythmia, both during traction and during anaesthesia, was similar also. The use of glycopyrrolate may be slightly advantageous, since the tachycardia produced by 7.5 $\mu g\,kg^{-1}$ was less than that produced by atropine 15 $\mu g\,kg^{-1}$. In this respect, our findings are similar to those of Meyers and Tomeldan (1979), with the exception that atropine produced a far greater degree of tachycardia in their study. This was a result of the fact that glycopyrrolate has not reached its peak effect by 1 min, the time Meyers and Tomeldan (1979) studied the effects of the two drugs on heart rate. Studies in anaesthetized adults (Mirakhur, Jones and Dundee, 1981) and in awake and anaesthetized children (Mirakhur and Jones, 1982) show the peak effect of glycopyrrolate is not achieved until 3–4 min following administration.

In conclusion, both atropine and glycopyrrolate are equally effective in the prevention of the oculocardiac reflex, particularly when higher doses were administered i.v. Glycopyrrolate was, however, associated with tachycardia of a smaller magnitude.

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## REFERENCES

Alexander, J. P. (1975). Reflex disturbances of cardiac rhythm during ophthalmic surgery. *Br. J. Ophthalmol.*, 59, 518.

Apt, L., Isenberg, B. A., and Gaffney, W. L. (1973). The oculocardiac reflex in strabismus surgery. *Am. J. Ophthalmol.*, **76,** 533.

Aserinsky, E., and Debias, D. A. (1963). Suppression of the oculocardiac reflex by artificial respiration. *Arch. Ophthalmol.*, **69,** 484.

Berler, D. K. (1963). The oculocardiac reflex. *Am. J. Ophthalmol.*, **56,** 954.

Bosomworth, P. P., Ziegler, C. H., and Jacoby, J. (1958). The oculocardiac reflex in eye muscle surgery. *Anesthesiology*, **19,** 7.

Deacock, A. R. de C., and Oxer, H. F. (1962). The prevention of reflex bradycardia during ophthalmic surgery. *Br. J. Anaesth.*, **34,** 451.

Dewar, K. M. S., and Wishart, H. Y. (1976). The oculocardiac reflex. *Proc. R. Soc. Med.*, **69,** 373.

Gandevia, S. C., McCloskey, D. I., and Potter, E. K. (1978). Reflex bradycardia occurring in response to diving, nasopharyngeal stimulation and ocular pressure and its modification by respiration and swallowing. *J. Physiol. (Lond.).*, **276,** 383.

Katz, R. L., and Bigger, J. T. jr (1970). Cardiac arrhythmias during anesthesia and operation. *Anesthesiology*, **33,** 193.

—— Katz, L. E. (1978). Cardiac arrhythmias associated with anaesthesia and operations; in *Haemodynamic Changes in Anaesthesia*, p. 1241. Paris: Academie Europeene d'Anesthésiologie.

Kwik, R. S. H. (1980). Marcus – Gunn Syndrome associated with an unusual oculo-cardiac reflex. *Anaesthesia*, **35,** 46.

Mendelblatt, F. J., Kirsch, R. E., and Lemberg, L. (1962). Preventing the oculocardiac reflex. *Am. J. Ophthalmol.*, **53,** 506.

Meyers, E. F., and Tomeldan, S. A. (1979). Glycopyrrolate compared with atropine in prevention of the oculocardiac reflex during eye-muscle surgery. *Anesthesiology*, **51,** 350.

Mirakhur, R. K., Clarke, R. S. J., Elliott, J., and Dundee, J. W. (1978). Atropine and glycopyrronium premedication: a comparison of the effects on cardiac rate and rhythm during induction of anaesthesia. *Anaesthesia*, **33,** 906.

—— Jones, C. J. (1982). Atropine and glycopyrrolate: changes in cardiac rate and rhythm in conscious and anaesthetized children. *Anaesth. Intens. Care*, (in press).

—— —— Dundee, J. W. (1981). Effects of intravenous administration of glycopyrrolate and atropine in anaesthetised patients. *Anaesthesia*, **36,** 277.

Moonie, G. T., Ress, D. L., and Elton, D. (1964). The oculocardiac reflex during strabismus surgery. *Can. Anaesth. Soc. J.*, **11,** 621.

Planten, J. T. (1963). Clinical observation of the oculocardiac reflex. *Opthalmologica*, **146,** 300.

Pontinen, P. J. (1966). The importance of the oculocardiac reflex during ocular surgery. *Acta Ophthalmol.* (Suppl.) 86.

Schwartz, H. (1971). Oculocardiac reflex: is prophylaxis necessary?; in *Highlights of Clinical Anesthesiology* (eds L. C. Mark and S. H. Ngai), p. 111. New York: Harper and Row.

## ATROPINE OU GLYCOPYRROLATE PAR VOIE I.M. OU I.V. POUR LA PREVENTION DU REFLEXE OCULOCARDIAQUE CHEZ DES ENFANTS SOUMIS A LA CHIRURGIE DU STRABISME

### RESUME

La fréquence et la nature du réflexe oculocardiaque ainsi que sa prévention par l'atropine ou le glycopyrrolate (i.m. et i.v.) ont été étudiées chez 160 enfants subissant une chirurgie de correction du strabisme. Quatre vingt dix pour cent des enfants n'ayant reçu aucune prémédication anticholinergique ont objectivé ce réflexe. Ceci a été réduit à environ 50% chez ceux dont la prémédication était i.m. Le glycopyrrolate, $7,5\,\mu g\,kg^{-1}$ i.v. et l'atropine $15\,\mu g\,kg^{-1}$ i.v. étaient le plus souvent efficaces, cette dernière étant légèrement supérieure. Cependant, le glycopyrrolate était associé à une tachycardie moins importante. Le réflexe était le plus souvent observé après une traction sur le muscle droit médian.

## INTRAMUSKULÄRES ODER INTRAVENÖSES ATROPIN ODER GLYKOPYRROLAT ZUR VERHINDERUNG DES OKULOKARDIALEN REFLEXES BEI KINDERN, DIE SICH EINER SCHIELOPERATION UNTERZIEHEN MUßTEN

### ZUSAMMENFASSUNG

Das Auftreten und die Art des okulokardialen Reflexes und seine Verhinderung durch Atropin oder Glykopyrrolat i.m. oder i.v. wurde bei 160 Kindern, die sich einer Schieloperation unterziehen mußten, untersucht. Bei 90% der Patienten, die keine anticholinergische Prämedikation erhalten hatten, trat der Reflex auf. Dieser verminderte sich auf 50% bei Prämedikation mit diesen Mitteln. Glykopyrrolat $7,5\,\mu g\,kg^{-1}$ und Atropin $15\,\mu g\,kg^{-1}$ waren in den meisten Fällen wirksam, das letzte etwas besser. Jedoch war bei Glykopyrrolat die Tachykardie weniger ausgeprägt. Der Reflex wurde bei Zug am M.rectus medialis öfter beobachtet.

## ATROPINA I.V. I.M. Ó GLICOPIRROLATO PARA PREVENIR EL REFLEJO OCULOCARDÍACO EN NIÑOS SOMETIDOS A CIRUJÍA POR ESTRABISMO

### SUMARIO

En 160 niños sometidos a cirujía para corregir el estrabismo, se estudió la frecuencia y la naturaleza del reflejo oculocardíaco y su prevención por atropina o glicopirrolato (i.m. e i.v.). Un noventa por ciento de los niños que no recibieron premedicación anticolinérgica experimentaron el reflejo. Este porcentaje se redujo hasta un 50% aproximadamente en los que recibieron las substancias i.m. En la mayoría de los casos, $7,5\,\mu g\,kg^{-1}$ de glicopirrolato y $15\,\mu g\,kg^{-1}$ de atropina tuvieron efecto, la última siendo ligeramente mejor. Sin embargo, el glicopirrolato se acompañó con taquicardia de menor amplitud. Se observó el reflejo más a menudo después de tracción sobre el músculo rectal medio.

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# DOES ATROPINE PREMEDICATION AFFECT THE CARDIOVASCULAR RESPONSE TO LARYNGOSCOPY AND INTUBATION?

A. FASSOULAKI AND P. KANIARIS

## SUMMARY

The effect of atropine premedication i.v. and i.m. on the cardiovascular changes resulting from laryngoscopy and tracheal intubation has been evaluated in 139 patients undergoing major surgery. Atropine administered i.v. and i.m. did not affect the hypertensive response to laryngoscopy and tracheal intubation, but did augment the tachycardia and increased the frequency of cardiac arrhythmia observed during intubation of the trachea.

The use of anticholinergic drugs in premedication remains controversial. Atropine, the traditional drug has been incriminated for producing cardiac arrhythmias, visual difficulties and decreasing the tone of the lower oesophageal sphincter (Cotton and Smith, 1981). On the other hand, laryngoscopy and tracheal intubation are accompanied by cardiovascular changes which are undesirable and may be dangerous in patients suffering from heart disease. In several of the techniques described to attenuate such cardiovascular responses an anticholinergic premedicant, usually atropine, has been used. The objective of this study was to investigate the effect of atropine premedication i.v. or i.m. on the responses to direct laryngoscopy and intubation of the trachea.

## PATIENTS AND METHODS

One hundred and thirty-nine patients scheduled for elective major surgery (hemicolectomy, abdominoperineal resection, modified radical mastectomy and cholecystectomy) participated. All were visited and assessed the night before the operation and their consent was obtained. No patient was receiving antiarrhythmic drugs, digoxin, hypotensive agents or beta-blocking drugs. Their e.c.g. were normal on admission to hospital.

The patients were randomly allocated to an i.v. group (73 patients) or an i.m. group (66 patients). The premedicants for both groups consisted of either atropine alone or normal saline alone. No narcotics or tranquillizers were administered, so that the effect of atropine on the cardiovascular response to laryngoscopy could be assessed precisely.

The patients in each group were again randomly allocated to two subgroups: the i.v.$_A$ group consisted of 38 patients who received atropine 0.6 mg i.v. in the anaesthetic room 5 min before the induction of anaesthesia. The i.v.$_{NS}$ group (35 patients) received one ampoule of normal saline (same volume as the ampoule of atropine), so that the anaesthetist was unaware of the drug given. The i.m.$_A$ group (36 patients) received atropine 0.6 mg i.m. 30 min before the induction of anaesthesia and the i.m.$_{NS}$ group (30 patients) received 1 ml of normal saline 30 min before induction of anaesthesia. The patients of these groups were similar with respect to age and weight. The mean age in the i.v.$_A$ group was 46.4 yr and in the i.v.$_{NS}$ group 46.5 yr. Groups i.m.$_A$ and i.m.$_{NS}$ had mean ages of 47.1 and 46.2 yr respectively. Mean body weights were 64.1 and 63.8 kg for the i.v.$_A$ and the i.v.$_{NS}$ groups respectively and 64.7 and 64 kg for the i.m.$_A$ and i.m.$_{NS}$ groups.

After a 5-min period in the anaesthetic room systolic arterial pressure (SAP) (Recklinhausen oscillotonometer) and heart rate (HR) were measured. Lead 2 electrocardiogram (e.c.g.) was displayed on an oscilloscope and connected to a pen recorder. An e.c.g. containing one or more ectopic beats was considered abnormal. After the initial recordings the patients were asked to breathe 100% oxygen through a mask and a needle was inserted into a vein on the back of the hand. The premedicant (atropine

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or normal saline) was administered i.v. if the patient was allocated to the i.v. group. Nothing was given to those patients who already had received an i.m. injection. Five minutes after the insertion of the needle the second readings of SAP and heart rate were recorded. Anaesthesia was induced with thiopentone 6 mg kg$^{-1}$ followed by suxamethonium 1 mg kg$^{-1}$ to facilitate tracheal intubation and readings were continued at 0 min (when the cuff of the tracheal tube was inflated), and at 5 and 10 min after intubation. Halothane and nitrous oxide in oxygen were given for the 10 min following intubation. During this time ventilation was controlled manually or assisted. Non-depolarizing neuromuscular blocking drugs and analgesics were administered after the last readings had been completed. Arterial blood-gas tensions obtained 3–5 min after intubation were measured on an ABL$_3$ (Copenhagen –Radiometer) blood-gas analyser.

Student's *t* test for paired observations was used for parametric data and the Chi-square test for non-parametric data.

## RESULTS

### *Systolic arterial pressure*

A significant increase in SAP ($P<0.001$) was observed in all the groups immediately after intubation of the trachea. SAP returned to baseline over the subsequent 5–10 min (table I).

### *Heart rate*

The changes in HR were most marked after atropine i.v. which produced a significant increase ($P<0.001$) at 0, 5 and 10 min after completion of intubation. The i.m.$_A$ group had the highest initial mean HR which increased further after intubation ($P<0.001$), becoming not significantly different from baseline 10 min after intubation. In the control groups (i.v.$_{NS}$ and i.m.$_{NS}$) significant but smaller increases ($P<0.001$) in HR were observed immediately after intubation. These changes were not significant by 5 and 10 min (table II).

TABLE I. *Mean ± SEM systolic arterial pressure (mm Hg) a: before premedication, b: 5 min after premedication i.v., or after the insertion of the i.v. needle in the i.m. groups, c: 0 min, d: 5 min and e: 10 min after intubation*

| | a | b | Time after intubation (min) | | |
|---|---|---|---|---|---|
| | Before premedication | 5 min after i.v. premedication | c: 0 | d: 5 | e: 10 |
| Group i.v.$_A$<br>($n = 38$) | 136 ± 2.62 | 141 ± 3.12<br>$P_{a-b}>0.10$ | 187 ± 5<br>$P_{a-c}<0.001$ | 143 ± 4.42<br>$P_{a-d}>0.10$ | 126 ± 2.51<br>$P_{a-e}<0.02$ |
| Group i.v.$_{NS}$<br>($n = 35$) | 144 ± 3.33 | 140 ± 3.33<br>$P_{a-b}>0.40$ | 182 ± 5<br>$P_{a-c}<0.001$ | 146 ± 4.29<br>$P_{a-d}>0.60$ | 130 ± 3.26<br>$P_{a-e}<0.01$ |
| Group i.m.$_A$<br>($n = 36$) | 134 ± 2.77 | 136 ± 2.79<br>$P_{a-b}>0.60$ | 188 ± 4.23<br>$P_{a-c}<0.001$ | 148 ± 4.54<br>$P_{a-d}<0.02$ | 125 ± 3.48<br>$P_{a-e}<0.05$ |
| Group i.m.$_{NS}$<br>($n = 30$) | 135 ± 3 | 130 ± 3<br>$P_{a-b}>0.20$ | 172 ± 4.35<br>$P_{a-c}<0.001$ | 135 ± 4.35<br>$P_{a-d}>0.90$ | 118 ± 3.6<br>$P_{a-e}<0.005$ |

TABLE II. *Mean ± SEM heart rates (beat min$^{-1}$) a: before premedication, b: 5 min after premedication i.v., or 5 min after the insertion of the i.v. needle in the i.m. groups, c: 0 min, d: 5 min and e: 10 min after intubation*

| | a | b | Time after intubation (min) | | |
|---|---|---|---|---|---|
| | Before premedication | 5 min after i.v. premedication | c: 0 | d: 5 | e: 10 |
| Group i.v.$_A$<br>($n = 38$) | 86 ± 1.93 | 108 ± 2.43<br>$P_{a-b}<0.001$ | 122 ± 2.68<br>$P_{a-c}<0.001$ | 105 ± 2.5<br>$P_{a-d}<0.001$ | 101 ± 2.42<br>$P_{a-e}<0.001$ |
| Group i.v.$_{NS}$<br>($n = 35$) | 91 ± 2.5 | 90 ± 2.52<br>$P_{a-b}>0.70$ | 104 ± 2.45<br>$P_{a-c}<0.001$ | 95 ± 2.30<br>$P_{a-d}>0.20$ | 86 ± 2.26<br>$P_{a-e}>0.10$ |
| Group i.m.$_A$<br>($n = 36$) | 95 ± 3 | 97 ± 2.88<br>$P_{a-b}>0.60$ | 117 ± 3.17<br>$P_{a-c}<0.001$ | 105 ± 2.81<br>$P_{a-d}<0.025$ | 100 ± 2.78<br>$P_{a-e}>0.20$ |
| Group i.m.$_{NS}$<br>($n = 30$) | 87 ± 1.8 | 86 ± 1.9<br>$P_{a-b}>0.60$ | 105 ± 2.51<br>$P_{a-c}<0.001$ | 90 ± 2.25<br>$P_{a-d}>0.30$ | 84 ± 2.30<br>$P_{a-e}>0.30$ |

### *Cardiac arrhythmias*

The cardiac arrhythmias observed were ventricular extrasystoles. Those patients who received atropine i.v. had a greater frequency of arrhythmia (52%) compared with the i.v.$_{NS}$ group (26%) and this difference was significant ($P < 0.05$). The administration of atropine i.m. 30 min before induction of anaesthesia also induced a significantly greater frequency of arrhythmia (58%) than the control group (30%) (table III).

TABLE III. *Frequency of cardiac arrhythmia in each of the four groups of patients*

| | No. patients with arrhythmia | % | Statistical evaluation |
|---|---|---|---|
| Group i.v.$_A$<br>($n = 38$) | 20 | 52 | $\chi^2 = 4.448$<br>$P_{\text{i.v.}} < 0.05$ |
| Group i.v.$_{NS}$<br>($n = 35$) | 9 | 26 | |
| Group i.m.$_A$<br>($n = 36$) | 21 | 58 | $\chi^2 = 4.22$<br>$P_{\text{i.m.}} < 0.05$ |
| Group i.m.$_{NS}$<br>($n = 30$) | 9 | 30 | |

The extrasystoles observed in each group of patients were: in the i.v.$_A$ group one to five ventricular extrasystoles in 12 patients (unifocal in eight patients and multifocal in four). Eight patients had more than five ectopic beats (three, unifocal ventricular extrasystoles, three bigeminus and two patients multifocal extrasystoles). In the i.v.$_{NS}$ group one to five unifocal ectopic beats were observed in five patients and in four patients more than five ventricular ectopic beats were observed (two patients developed bigeminus and two unifocal ventricular extrasystoles). In the i.m.$_A$ group one to five ventricular extrasystoles were observed in eight patients and more than five extrasystoles in 13 patients (five patients had bigeminus, five had unifocal and three patients had multifocal ectopic beats). In one patient cardiac arrhythmia started as multifocal ventricular extrasystoles followed by bigeminus and continued as ventricular extrasystoles. In the i.m.$_{NS}$ group six patients had one to five ventricular extrasystoles (unifocal) and three patients more than five ventricular ectopic beats (two bigeminus and one multifocal).

The mean values of blood-gas tensions for each group of patients 3–5 min after intubation were: i.v.$_A$ group, $Pa\text{O}_2$ 24.9 kPa and $Pa\text{CO}_2$ 4.6 kPa; i.v.$_{NS}$ group, $Pa\text{O}_2$ 24.5 kPa and $Pa\text{CO}_2$ 4.6 kPa; i.m.$_A$ group, $Pa\text{O}_2$ 24.5 kPa and $Pa\text{CO}_2$ 4.6 kPa; i.m.$_{NS}$ group, $Pa\text{O}_2$ 25.9 kPa and $Pa\text{CO}_2$ 4.4 kPa.

## DISCUSSION

Cardiovascular instability following laryngoscopy and tracheal intubation has been investigated extensively and different techniques have been used to prevent these effects: laryngeal and oropharyngeal local anaesthesia (Abou-Madi, Keszler and Yacoub, 1975), oropharyngeal viscous lignocaine before laryngoscopy (Stoelting, 1978), alpha- and beta-blocking agents (De Vault, Greifenstein and Harris, 1960; Prys-Roberts et al., 1973; Curran, Crowley and O'Sullivan, 1980; Werner et al., 1980). In all these techniques an anticholinergic premedicant was given routinely and the beta-blocking drugs were preceded by a generous dose of atropine to prevent bradycardia (Prys-Roberts et al., 1973; Werner et al., 1980).

The question arises, does atropine affect the cardiovascular changes caused by laryngoscopy and intubation? The present study demonstrated that atropine administered either i.v. or i.m. does not affect the hypertensive response to laryngoscopy and intubation, but increases the tachycardia and the frequency of cardiac arrhythmia resulting from laryngoscopy and intubation.

The chronotropic effect of the drug is closely related to the plasma concentration and the peak concentration in plasma is obtained at 30 min. The onset of antisialagogue action is slower, reaching its peak about 100 min after i.m. administration (Berghem et al., 1980). Although Mirakhur and colleagues (1978), in a smaller number of patients, observed an increase in the occurrence of cardiac arrhythmias, their frequency (35%) was substantially less than that observed in the present study (58%). Ninety minutes elapsed between the i.m. injection and the induction of anaesthesia in their study and could explain this difference, since by that time the effect of atropine in increasing the heart had passed while the peak effect on salivation had been reached.

In the present study the groups not receiving atropine did not have any specific problems with secretions. This is as expected in minor operations (Mirakhur, Dundee and Connolly, 1979). Nevertheless, in all our patients the trachea was intubated and the operations performed were major.

The authors recommend omitting atropine as a premedicant to eliminate the additional effect on heart rate and the increase in the frequency of cardiac arrhythmia which occurs usually in association with laryngoscopy and tracheal intubation and which is augmented by the administration of atropine. In patients with decreased myocardial reserve a single injection of a small dose of sodium nitroprusside i.v. attenuates the increase in arterial pressure during tracheal intubation (Stoelting, 1979). By omitting atropine and administering small doses of droperidol and fentanyl i.v. 5 min before anaesthesia, the cardiovascular changes resulting from intubation are minimized (Fassoulaki, Kaniaris and Kotsanis, 1981). Adrenergic blocking drugs should be administered a few days before operation (Fassoulaki, Kaniaris and Kotsanis, 1980) since a single dose of a beta-blocking drug shortly before anaesthesia has no effect on the hypertensive response to laryngoscopy (Werner et al., 1980). The reason is that there is no direct relation between the plasma concentration of a beta-blocking drug and its anti-hypertensive effect (Tarazi and Dustan, 1972). If the antihypertensive effect of a beta-blocker is desirable, the drug should be given a few days before anaesthesia (Conway and Amery, 1975). Nonetheless, as the degree of blockade of heart rate by beta-blocking drugs is closely related to the plasma concentrations of the drug (Vaughan-Williams et al., 1975), the administration of a beta-blocker i.v. before the induction of anaesthesia will prevent the tachycardia and arrhythmias associated with laryngoscopy while the hypertensive response will be unaffected. The administration of a beta-blocking drug i.v. shortly before anaesthesia preceded by a generous dose of atropine, as recommended by Prys-Roberts and colleagues (1973) seems unjustifiable because the hypertensive response is not affected, while the beta-blockade attenuates the tachycardia and arrhythmias already enhanced by atropine.

Routine anticholinergic premedication needs reevaluation (Mirakhur et al., 1978). The present study establishes the harmful effect of premedication with atropine. Since sympathetic activity predominates during laryngoscopy and intubation of the trachea, protection against vagal over-activity may be unnecessary.

We would advise omitting atropine as a premedicant, as a first step, and then consideration of by what other means one could attenuate the cardiovascular response to direct laryngoscopy and intubation of the trachea.

## REFERENCES

Abou-Madi, M., Keszler, H., and Yacoub, O. (1975). A method for prevention of cardiovascular responses to laryngoscopy and intubation. *Can. Anaesth. Soc. J.*, 22, 316.

Berghem, L., Bergman, B., Schildt, B., and Sörbo, B. (1980). Plasma atropine concentrations determined by radioimmunoassay after single-dose i.v. and i.m. administration. *Br. J. Anaesth.*, 52, 597.

Conway, J., and Amery, A. (1975). The antihypertensive effect of propranolol and other β-adrenoceptor antagonists; in *Central Action of Drugs in Regulation of Blood Pressure* (eds D. Davies and J. Reid), p. 277. London: Pitman Medical Publishing Co Ltd.

Cotton, B. R., and Smith, G. (1981). Anticholinergic premedication and regurgitation. *Br. J. Anaesth.*, 53, 445.

Curran, J., Crowley, M., and O'Sullivan, G. (1980). Droperidol and endotracheal intubation. Attenuation of pressor response to laryngoscopy and intubation. *Anaesthesia*, 35, 290.

De Vault, M., Greifenstein, F. E., and Harris, L. C. (1960). Circulatory responses to endotracheal intubation in light general anesthesia—the effect of atropine and phentolamine. *Anesthesiology*, 21, 360.

Fassoulaki, A., Kaniaris, P., and Kotsanis, S. (1980). Atenolol pretreatment in fiberoptic bronchoscopy: effect on cardiac arrhythmias, heart rate and arterial blood pressure. *Acta Anaesthesiol. Belg.*, 31, 279.

—— —— —— (1981). Effect of premedicants on the cardiovascular system. Is premedication with atropine necessary? *Proceedings of the 3rd Scientific Meeting of the European Academy of Anaesthesiology*, Vienna, 1981 (in press). Berlin, Heidelberg, New York: Springer-Verlag.

Mirakhur, R. K., Clarke, R. S. J., Elliot, J., and Dundee, J. W. (1978). Atropine and glycopyrronium premedication. *Anaesthesia*, 33, 906.

—— Dundee, J. W., and Connolly, J. D. R. (1979). Studies of drugs given before anaesthesia. XVII: Anticholinergic premedicants. *Br. J. Anaesth.*, 51, 339.

Prys-Roberts, C., Föex, P., Biro, G. P., and Roberts, J. G. (1973). Studies of anaesthesia in relation to hypertension. V: Adrenergic beta receptor blockade. *Br. J. Anaesth.*, 45, 671.

Stoelting, R. K. (1978). Blood pressure and heart rate changes during short-duration laryngoscopy for tracheal intubation: influence of viscous or intravenous lidocaine. *Anesth. Analg. (Cleve.)*, 57, 197.

—— (1979). Attenuation blood pressure response to laryngoscopy and tracheal intubation with sodium nitroprusside. *Anesth. Analg. (Cleve.)*, 58, 116.

Tarazi, R. C., and Dunstan, H. P. (1972). Beta adrenergic blockade in hypertension. Practical and theoretical implications of long-term hemodynamic variations. *Am. J. Cardiol.*, 29, 633.

Vaughan Williams, E. M., Raine, A. E. G., Cabrera, A. A., and Whyte, J. M. (1975). The effects of prolonged β-adrenoreceptor blockade on heart weight and cardiac intracellular potentials in rabbits. *Cardiovasc. Res.*, 9, 579.

Werner, O., Magnusson, J., Fletcher, R., Nilsson-Ehle, P., and Palm, O. (1980). Practolol during microlaryngoscopy. Effect on arterial pressure, heart rate, blood glucose and lipolysis. *Br. J. Anaesth.*, 52, 91.

## LA PREMEDICATION PAR L'ATROPINE MODIFIE-T-ELLE LA RESPONSE CARDIOVASCULAIRE A LA LARYNGOSCOPIE ET A L'INTUBATION?

### RESUME

Nous avons étudié les effets de la prémédication par l'atropine i.m. et i.v. sur les modifications cardiovasculaires dues à la laryngoscopie et à l'intubation trachéale chez 139 patients subissant une chirurgie majeure. L'atropine administrée par voie i.m. et i.v. ne modifie pas la réponse hypertensive à la laryngoscopie et à l'intubation endotrachéale mais elle augmente la tachycardie et la fréquence es troubles du rythme observés au cours de l'intubation endotrachéale.

## BEINFLUSST DIE PRÄMEDIKATION MIT ATROPIN DIE KARDIOVASKULÄRE REAKTION AUF DIE LARYNGOSKOPIE UND INTUBATION?

### ZUSAMMENFASSUNG

Die Wirkung der Prämedikation mit Atropin i.v und i.m auf die durch die Laryngoskopie und Trachealintubation verursachten Einflüsse auf das kardiovaskuläre System wurde bei 139 Patienten, die sich einer größeren Operation unterziehen mußten, gemessen. Atropin i.v. und i.m. beeinflußt die hypertensive Reaktion auf die Laryngoskopie und Trachealintubation nicht, verstärkt aber die Tachykardie und das Auftreten von Herzarrythmien während der Trachealintubation.

## AFECTA LA PREMEDICACIÓN POR ATROPINA LA RESPUESTA CARDIOVASCULAR A LA LARINGOSCOPIA Y LA INTUBACIÓN?

### SUMARIO

Se procedió a la evaluación del efecto de la premedicación por atropina i.v. e i.m. sobre los cambios cardiovasculares resultantes de una laringoscopia y de una intubación traqueal en 139 pacientes sometidos a operaciones quirúrgicas mayores. La atropina administrada por vía i.v. e i.m. no afectó la respuesta hipertensiva a la laringoscopia y a la intubación traqueal, pero sí hizo aumentar la taquicardia e incrementar la frecuencia de la arritmia cardíaca observada durante la intubación de la tráquea.

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# PREOPERATIVE STARVATION AND BLOOD GLUCOSE CONCENTRATIONS IN CHILDREN UNDERGOING INPATIENT AND OUTPATIENT ANAESTHESIA

B. H. JENSEN, M. WERNBERG AND M. ANDERSEN

## SUMMARY

Blood glucose concentrations were measured in 82 children undergoing inpatient anaesthesia and in 46 children undergoing anaesthesia as outpatients. The children were aged between 6 months and 9 yr. Outpatients were fasted from bedtime, while inpatients were randomly allocated to two groups. In group A the children were fasted from bedtime, whereas in group B the children were fed 6 h before anaesthesia. There was no difference in mean blood glucose concentration between the fasted inpatients and outpatients nor between children younger than, or older than, 4 years of age. A blood glucose concentration of less than 40 mg dl$^{-1}$ was found in only one of the fasted children (1%). The mean blood glucose concentration was greater in group B than A, but only significantly so for children older than 4 yr. It is concluded that to minimize the risks of hypoglycaemia and inhalation of vomit on induction of anaesthesia children older than 6 months should be fasted overnight and operated on in the morning.

Since the risks of vomiting, and the inhalation of gastric contents, are inherent in the administration of general anaesthesia, established practice ordains that no patient for elective surgery be anaesthetized without a period of starvation and fluid deprivation. This period varies from 6 to 12 h or even more, in different institutions.

In studies of prolonged starvation adults were able to sustain normal glycaemic values (Cahill et al., 1966). The risk of hypoglycaemia from prolonged preoperative starvation in children was investigated by Thomas (1974), who studied the blood glucose concentrations on induction of anaesthesia in two groups of children and introduced feeding regimes in which children under 4 yr received milk or fruit syrup 4–6 h before operation.

In another study in children younger than 5 yr undergoing outpatient anaesthesia, no patient had a blood glucose concentration less than 40 mg dl$^{-1}$, despite at least 8 h starvation (Graham, 1979).

The purpose of the present study was to investigate the blood glucose concentrations in children undergoing inpatient and outpatient anaesthesia who were fasted and in children who received fruit syrup 6 h before inpatient anaesthesia.

## PATIENTS AND METHODS

### *Patients*

One hundred and thirty-four otherwise healthy children, aged 6 months to 9 yr, and scheduled for elective minor surgery such as tonsillectomy, adenoidectomy and myringotomy were included in the study. The parents were informed of the purpose of the investigation and all gave their consent.

The children formed two main groups: 88 children were inpatients and 46 children were outpatients operated by a specialist outside the hospital. Each of the main groups was subdivided further into two sub-groups, group I consisting of children younger than 4 yr and group II of children greater than 4 yr.

Outpatients were all fasted from bedtime. Inpatients in both groups were randomly allocated such that some of the children were fasted from bedtime (group A) whereas others received fruit syrup and water in a dose of 7.5 ml kg$^{-1}$ 6 h before anaesthesia (group B). The fruit syrup and water contained invertose 20 g dl$^{-1}$. Six children less than 4 yr refused to take the fruit syrup and were discharged from the study.

The ages, body weights and durations of starvation in the various groups are given in table I.

### *Anaesthesia*

All children were anaesthetized in the morning. Inpatients were premedicated with nicomorphine

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TABLE I. *Age, body weight, duration of starvation and blood glucose concentration before operation in 82 children undergoing inpatient and 46 children undergoing outpatient anaesthesia. Group I: Children younger than 4 yr, II: Children older than 4 yr; A: Fasting from bedtime, B: Received fruit syrup 6 h before anaesthesia. Mean values ± 1 SD and range (in parentheses)*

| Group | *n* | Age (yr) | Body weight (kg) | Duration of starvation (h) | Blood glucose concentration (mg dl$^{-1}$) |
|---|---|---|---|---|---|
| Inpatients | | | | | |
| I-A | 24 | 2.2±0.9 | 13.0±2.3 | 12.9±1.6 | 74±10 |
| | | (0.8–3.8) | (8–17) | (7–16) | (55–102) |
| I-B | 15 | 1.9±0.9 | 12.5±2.2 | | 76± 9 |
| | | (0.5–3.8) | (9–17) | | (65–90) |
| II-A | 22 | 5.9±1.7 | 21.3±4.9 | 13.6±1.5 | 72±16 |
| | | (4–9) | (14–32) | (11–17) | (32–96) |
| II-B | 21 | 5.9±1.6 | 21.8±4.9 | | 82±10 |
| | | (4–9) | (14–34) | | (73–106) |
| Outpatients | | | | | |
| I | 25 | 2.3±0.8 | 13.5±2.0 | 13.5±1.9 | 70± 7 |
| | | (0.7–3.5) | (9–17) | (8–16) | (55–84) |
| II | 21 | 5.7±1.7 | 20.9±4.4 | 14.5±2.0 | 70± 6 |
| | | (4–9) | (14–30) | (12–19) | (59–81) |

(Vilan) 0.2 mg kg$^{-1}$ and atropine 0.01 mg kg$^{-1}$. Outpatients received no premedication. Outpatients were accompanied by a parent during the induction of anaesthesia, whereas this was not the case in inpatients. All children were anaesthetized by the inhalation of halothane in an oxygen–nitrous oxide mixture.

### *Measurement of blood glucose concentration*

Immediately after the disappearance of the eylash reflex blood samples were withdrawn from a cubital vein. Just before venepuncture a tourniquet was placed. All venepunctures were performed by well-trained personnel. Samples were collected into fluoride bottles and analysed immediately by the o-toluidine method (Feteris, 1965). The mean of two measurements was determined. Hypoglycaemia was defined as a blood glucose concentration less than 40 mg dl$^{-1}$.

### *Statistics*

The differences between groups were tested by Student's *t* test. The correlation between the period of starvation and the blood glucose concentration was estimated by Spearman's rank correlation coefficient. *P* values less than 0.05 were considered significant.

## RESULTS

The mean values of the blood glucose concentrations in the different groups are given in table I. The distribution of blood glucose concentrations in all the fasted children is depicted in figure 1.

Inpatients and outpatients were comparable with respect to age and body weight whether less than, or greater than, 4 yr (groups I and II). Fasted inpatients and all outpatients were comparable with respect to their durations of starvation.

There were no differences in mean blood glucose

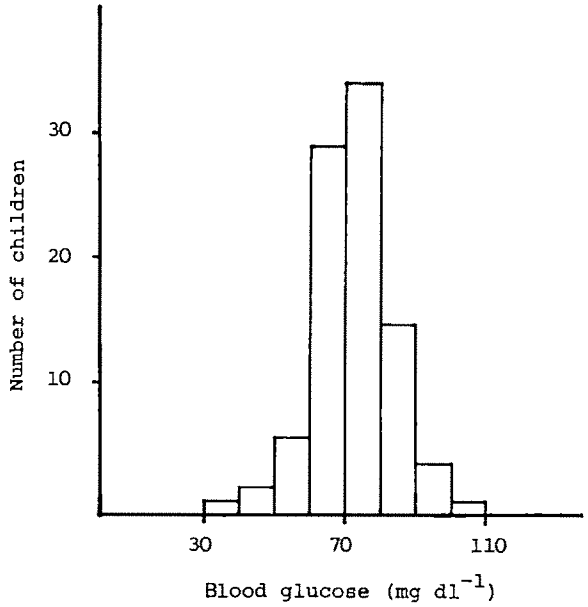

FIG. 1. Distribution of blood glucose concentrations in 92 children fasted before operation.

concentrations between the fasted inpatients (group A) and outpatients less than 4 yr ($P > 0.1$, $t = 1.34$) or greater than 4 yr ($P > 0.5$, $t = 0.58$). Likewise, there were no differences in mean blood glucose concentrations either when fasted (group A) inpatient children of groups I and II were compared ($P > 0.7$, $t = 0.34$) or when outpatients of groups I and II were compared ($P > 0.8$, $t = 0.14$).

In group I inpatients (less than 4 yr) there was no difference in mean blood glucose concentrations between groups A and B ($P > 0.3$, $t = 0.87$). However, the mean blood glucose concentration was significantly greater in group B than A in inpatients older than 4 yr (group II) ($0.02 < P < 0.03$, $t = 2.42$).

Hypoglycaemia occurred in one patient in group II-A, but not in any of the other groups. Thus, the frequency of hypoglycaemia in fasted inpatients was 2%, and in all fasted children 1%. The blood glucose concentrations in all fasted children were distributed according to a Gaussian curve (fig. 1), the distribution of the points, after probit transformation, being linear.

There was no correlation between the duration of the period of starvation and the blood glucose concentration in any of the fasted groups. For all fasted children the correlation coefficient was $r = -0.12$, $P > 0.10$.

There was no vomiting or regurgitation in either group during the induction of anaesthesia.

## DISCUSSION

After the 3rd day of life hypoglycaemia is most commonly defined as a blood glucose concentration of less than 40 mg dl$^{-1}$ (Cornblath and Schwartz, 1976; Habbick, McNeish and Stephenson, 1971).

The results of the present study are different from those obtained by Thomas (1974). In 18 children younger than 47 months he found a mean blood glucose concentration of $46.4 \pm 16.5$ mg dl$^{-1}$ and 28% of the children were hypoglycaemic. The children were premedicated with trimeprazine, anaesthetized with thiopentone and the blood samples were withdrawn from the long saphenous vein, all of which differ from the present study. The effect of these differences on blood glucose concentrations is unknown, so caution must be exercised when comparing the results. The most obvious difference is that in the present study all the children were anaesthetized in the morning, while all the children in the study of Thomas (1974) were anaesthetized in the afternoon. It may be that starvation is better tolerated during the night than during the morning because of diurnal variations in metabolism. This agrees with the study of Graham (1979), who in the same hospital and using the same technique of anaesthesia as Thomas (1974) found a mean blood glucose concentration of $74 \pm 3$ mg dl$^{-1}$ and no cases of hypoglycaemia following overnight fasting in 31 children less than 5 yr undergoing outpatient anaesthesia in the morning. However, contrary to the hypothesis proposed by Graham (1979), we could find no differences in mean glucose concentration between the fasted inpatients and the outpatients.

The only instance of hypoglycaemia occurred in a fasted 15-kg male child (50 months), who showed no clinical signs of hypoglycaemia before anaesthesia. The size of the child could be related to the study by Thomas (1974) since he described hypoglycaemia only in children of less than 15.5 kg body weight. According to the normal distribution of the blood glucose values in children fasting overnight, there may be a risk of hypoglycaemia during surgery. Much of this risk, however, may be avoided by adequate use of i.v dextrose during operation. In agreement with other studies (Watson, 1972; Serafimovski and Ibler, 1978; Graham, 1979) there was no correlation between the duration of the period of starvation and the blood glucose concentration.

In agreement with studies by Bevan and Burn (1973) and Thomas (1974) higher values of mean glucose concentrations were found in the groups who had been fed 6 h before anaesthesia. Thomas (1974) suggested that preoperative feeding is indicated particularly in children younger than 4 yr and weighing less than 15.5 kg, but in the present study this group showed no significant difference in mean blood glucose concentrations between the fasted and the fed children. In addition, six (29%) of the children in this group refused to receive fruit syrup in the middle of the night. Thus, preoperative feeding regimes for children older than 6 months of age, who are undergoing general anaesthesia in the morning, are of minor importance and cannot be recommended when one considers the risk of pulmonary aspiration of gastric contents. Further investigations are needed to determine the value of preoperative feeding of children less than 6 months of age.

In conclusion, to minimize the risk of hypoglycaemia and inhalation of vomit on the induction of anaesthesia, children older than 6 months should be fasted overnight and operated on in the morning.

ACKNOWLEDGEMENTS

We are indebted to Miss P. Michelsen and Mrs B. Skotte for skilled technical assistance, to Dr J. Kröyer Hansen and the staff in the department of otolaryngology for selection of the patients and Mrs N. Lund for secretarial assistance.

REFERENCES

Bevan, J. C., and Burn, M. C. (1973). Acid–base changes and anaesthesia. The influence of pre-operative starvation and feeding in paediatric surgical patients. *Anaesthesia*, **28**, 415.

Cahill, G. F., Herrera, M. G., Morgan, A. P., Soeldner, J. S., Steinke, J., Levy, P. L., Reichard, G. A., and Kipnis, D. M. (1966). Hormone–fuel interrelationships during fasting. *J. Clin. Invest.*, **45**, 1751.

Cornblath, M., and Schwartz, R. (1976). *Disorders of Carbohydrate Metabolism in Infancy*, 2nd edn, p. 345. Philadelphia: Saunders.

Feteris, W. A. (1965). A serum glucose method without protein precipitation. *Am. J. Med. Technol.*, **31**, 17.

Graham, I. F. M. (1979). Preoperative starvation and plasma glucose concentrations in children undergoing outpatient anaesthesia. *Br. J. Anaesth.*, **51**, 161.

Habbick, B. F., McNeish, A. S., and Stephenson, J. P. B. (1971). Diagnosis of ketotic hypoglycaemia of childhood. *Arch. Dis. Child.*, **46**, 295.

Serafimovski, N., and Ibler, M. (1978). Blood glucose levels in patients after preoperative fasting. *Ugeskr. Laeg.*, **140**, 1691.

Thomas, D. K. M. (1974). Hypoglycaemia in children before operation: its incidence and prevention. *Br. J. Anaesth.*, **46**, 66.

Watson, B. G. (1972). Blood glucose levels in children during surgery. *Br. J. Anaesth.*, **44**, 712.

## JEUNE PRE-OPERATOIRE ET GLYCEMIE CHEZ DES ENFANTS SOUMIS A DES ANESTHESIES, QU'ILS S'AGISSE DE PATIENTS HÔPITALISÉS OU AMBULATORES

### RESUME

Nous avons mesuré la glycémie de 82 enfants hôpitalisés et de 46 enfants ambulatoires soumis à une anesthésie. L'âge des enfants était situé entre 6 mois et 9 ans. Les patients ambulatoires jeûnaient toute la nuit, et les enfants hôpitalisés étaient répartis de façon aléatoire en 2 groupes. Dans le groupe A, les enfants jeûnaient toute la nuit, tandis que dans le groupe B les enfants étaient nourris 6 h avant l'anesthésie. Il n'y a pas eu de différences entre la glycémie moyenne des enfants ambulatoires et hôpitalisés qui avaient jêuné, ni entre la glycémie moyenne des enfants âgés de moins de 4 ans ou de plus de 4 ans. On n'a retrouvé une glycémie inférieure à 0,40 mg dl$^{-1}$ que chez un des enfants qui avaient jeûné (1%). La glycémie moyenne était plus élevée dans le groupe B que dans le groupe A mais ceci n'était significatif que pour les enfants de plus de 4 ans. Nous en concluons que pour minimiser le risque d hypoglycémie et d'inhalation de vomitus á l'induction de l'anesthéie, il faut faire jeûner toute la nuit les enfants de plus de 6 mois et les opérer le matin.

## PRÄOPERATIVES HUNGERN UND BLUTGLUKOSEKONZENTRATIONEN VON KINDERN BEI AMBULANTER UND NICHTAMBULANTER NARKOSE

### ZUSAMMENFASSUNG

Die Blutglukosekonzentrationen wurden bei 82 hospitalisierten Kindern und bei 46 Kindern, die eine ambulante Narkose erhielten, bestimmt. Die Kinder waren im Alter zwischen 6 Monaten und 9 Jahren. Die ambulanten Patienten mußten vom Zeitpunkt des Zubettgehens fasten, während die hospitalisierten nach Randomisierung in zwei Gruppen eingeteilt wurden. In Gruppe A mußten die Kinder vom Zubettgehen an fasten, während die kinder von Gruppe B 6 Stunden vor der Narkose Essen erhielten. Es gab keinen Unterschied zwischen den mittleren Blutglukosekonzentrationen der ambulanten und nichtambulanten Kinder die gefastet hatten, und auch nicht zwischen den Altersgruppen kleiner und größer als 4 Jahre. Eine Blutglukosekonzentration unter 40 mg dl$^{-1}$ wurde bei nur einem der Kinder die gefastet hatten, gefunden (1%). Die mittlere Blutglukosekonzentration war in Gruppe B höher als in Gruppe A, aber signifikant nur für Kinder über 4 Jahre. Daraus kann man schließen, daß, um die Risiken der Hypoglykämie und der Aspiration von Erbrochenem bei der Narkoseeinleitung möglichst gering zu halten, Kinder über 6 Monate über Nacht fasten und am Morgen operiert werden sollten.

## INANICIÓN PREOPERATORIA Y CONCENTRACIONES DE GLUCOSA EN LA SANGRE DE NIÑOS SOMETIDOS A ANESTESIA INTERNADOS EN HOSPITALES Y NO-HOSPITALIZADOS

### SUMARIO

Se midío las concentraciones de glucosa en la sangre de 82 niños sometidos a anestesia e internados en el hospital así como en la de 46 niños sometidos a anestesia y no-hospitalizados. La edad de los niños variaba entre 6 meses y 9 años. Los niños no-hospitalizados estuvieron de ayunas desde la víspera al momento de acostarse, mientras que los niños hospitalizados estuvieron repartidos al azar en dos grupos. En el grupo A, los niños estuvieron de ayunas desde la víspera al momento de acostarse y los del grupo B recibieron comida 6 horas antes de la anestesia. No hubo diferencia en la concentración media de glucosa en la sangre de los niños hospitalizados y no-hospitalizados de ayunas ni tampoco entre los niños menores o mayores de 4 años. Se verificó una concentración de glucosa en la sangre de menos de 40 mg dl$^{-1}$ en uno solo de los niños de ayunas (1%). La concentración media de glucosa en la sangre fue mayor en el grupo B que en el grupo A, pero de manera significante solamente en niños mayores de 4 años. Se llega a la conclusión que, para minimizar los riesgos de hipoglicemia e inhalación del vómito durante la inducción de la anestesia en los niños mayores de 6 meses, es necesario mantenerlos de ayunas desde la noche anterior y operarlos en la mañana.

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# INFLUENCE OF PREMEDICATION ON PLASMA ACTH AND CORTISOL CONCENTRATIONS IN CHILDREN DURING ADENOIDECTOMY

G. SIGURDSSON, S. LINDAHL AND N. NORDÉN

## SUMMARY

The endocrine response to stress, as reflected by the plasma concentrations of ACTH and cortisol, was investigated in 14 children receiving two different premedications during halothane anaesthesia for adenoidectomy. Seven children (group A) were premedicated with diazepam 5 mg rectally and atropine 0.3–0.4 mg sublingually and seven (group B) received a rectal combination of diazepam 0.5 mg $kg^{-1}$, morphine 0.15 mg $kg^{-1}$ and hyoscine 0.01 mg $kg^{-1}$. Before and after surgery plasma concentrations of ACTH and cortisol were lower in group B than in group A. In group A mean values for ACTH increased from 40.7 ng $litre^{-1}$ before adenoidectomy to 352.9 ng $litre^{-1}$ ($P<0.001$) after adenoidectomy. The corresponding increase in group B was from 12.1 ng $litre^{-1}$ to 82.1 ng $litre^{-1}$ ($P<0.01$). In group A mean cortisol concentrations increased from 235.7 nmol $litre^{-1}$ to 655.7 nmol $litre^{-1}$ after adenoidectomy ($P<0.001$) and in group B from 121.4 nmol $litre^{-1}$ to 427.9 nmol $litre^{-1}$ ($P<0.01$). End-tidal carbon dioxide tension was approximately the same in both groups. It was concluded that the combination of diazepam, morphine and hyoscine decreased the endocrine response to stress.

Although the plasma concentrations of ACTH and cortisol are increased during surgery (Sandberg, Eik-Nes and Samuels, 1954; Hume, Bell and Barter, 1962; Ichikawa et al., 1971) this response can be obtunded by high doses of morphine and fentanyl, and by extradural anaesthesia (George et al., 1974; Engqvist et al., 1977; Hall et al., 1978; Brandt et al., 1978). Since the influence of premedication on the endocrine response to preoperative anxiety and to surgical stimuli, as reflected by plasma concentrations of ACTH and cortisol, has not been reported previously, this study compared the plasma concentrations of ACTH and cortisol following the administration of two different premedications to children undergoing adenoidectomy.

## PATIENTS AND METHODS

Fourteen children scheduled for adenoidectomy were studied, none of whom had any evidence of acute infection, cardiac failure or pulmonary disease. All the children were fasted overnight and were randomly divided into two equal groups, A and B. In group A the mean age was 5 (range 3–7) yr with a mean body weight of 20.4 ± 3.2 (SD) kg and in group B, mean age was 4 (range 3–6) yr with a mean body weight of 17.1 ± 2.5 (SD) kg. The children in group A were premedicated with diazepam 5 mg (Stesolid) rectally, that is about 0.25 mg $kg^{-1}$, and atropine 0.3–0.4 mg sublingually 20–40 min before the induction of anaesthesia. Group B was premedicated with a rectal solution of diazepam (Apozepam) 0.5 mg $kg^{-1}$, morphine 0.15 mg $kg^{-1}$ and hyoscine 0.01 mg $kg^{-1}$, 30–40 min before the induction of anaesthesia.

Subsequently, whilst the child was still awake and in the presence of one of the parents, e.c.g. electrodes were applied. A photoelectric transducer (Siemens–Elema, Stockholm) (Baselius and Nordström, 1971), for assessment of capillary perfusion, was attached to the distal part of the flexor side of the thumb and an arterial pressure cuff of appropriate size was placed around the left arm.

Both groups were anaesthetized by the same anaesthetist, who was not informed of the premedication used. Before induction of anaesthesia the anaesthetist evaluated the sedative effect of the premedication according to a modification of the method described by Barker and Nisbet (1973) (table I). During induction the anaesthetist also evaluated the antisialagogue effect as adequate (0) or inadequate (−). Inhalation anaesthesia with nitrous oxide in oxygen ($FI_{O_2}$ 0.5) and halothane (maximum concentration 2.5%) was used. An oral endotracheal tube was inserted in all of the children without the

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TABLE I. *Evaluation of premedication*

| | | Score |
|---|---|---|
| (I) | Behaviour of the child | |
| | Crying or struggling | 0 |
| | Calm | 1 |
| | Sedated | 2 |
| | Drowsy | 3 |
| | Sleeping but arousable | 4 |
| (II) | Reaction to induction of anaesthesia | |
| | Crying or struggling | 0 |
| | Wincing or vocalizing | 1 |
| | Moving the hands or head | 2 |
| | None | 3 |
| Estimation of sedation (I + II) | | |
| | 0–1.9 = poor | |
| | 2–3.9 = fair | |
| | 4–5.9 = good | |
| | 6–7.9 = excellent | |

use of neuromuscular blocking drugs. Respiration was spontaneous. Rotameters for oxygen and nitrous oxide, and the Mark III halothane vaporizer, were calibrated. A Mapleson D circuit with fresh gas flows of three times the minute ventilation of the child was used to avoid rebreathing. During the induction of anaesthesia an infra-red carbon dioxide analyser (Siemens-Elema, Stockholm, 130) (Olsson et al., 1980) was incorporated in the anaesthetic circuit.

E.c.g., capillary perfusion (CP) and end-tidal carbon dioxide tension ($P\text{E}'\text{CO}_2$) were recorded continuously (Siemens–Elema, EM81). Heart rate (HR) and breathing frequency were calculated from e.c.g. recordings and end-tidal carbon dioxide curves, respectively. Systolic and diastolic arterial pressures were measured intermittently and the mean arterial pressure (m.a.p.) calculated. The carbon dioxide analyser was calibrated using two test gases of known carbon dioxide concentration. Because of dispersion of the infra-red spectrum by nitrous oxide, all carbon dioxide values were corrected by a factor of 0.95 which referred to 50% nitrous oxide.

After the induction of anaesthesia a vein on the extensor side of the hand was cannulated to allow blood sampling. Samples for the measurement of ACTH and cortisol concentrations were collected in test tubes containing EDTA (10.5 mg/7 ml blood) and aprotinin (Trasylol, Bayer, Germany, 3000 KIE/7 ml blood) which had been pre-chilled on ice-water. The samples were kept at 0 °C until centrifugation in a refrigerated centrifuge. The supernatants were then stored at −20 °C. The concentration of ACTH was determined by radioimmunoassay (ACTHK, Sorin Biomedica, Italy) using rabbit antiserum raised against porcine ACTH coupled to bovine albumin. Human ACTH was used as standard and $^{125}$I–ACTH as tracer. The coefficient of variation in duplicate determinations was 17% for values less than 50 ng $\text{litre}^{-1}$ and 10% for values greater than 50 ng $\text{litre}^{-1}$ (Hedner, Nordén and Valdemarsson, 1981). Cortisol concentration was determined using a solid phase radioimmunoassay (Gammacoat, Clinical Assays, Mass., U.S.A.) with rabbit anti-cortisol serum attached to the test tubes as binding protein and $^{125}$I-cortisol as tracer. The coefficient of variation was less than 7%. The cross reactivity was 88% for prednisolone and insignificant for other steroids tested.

Blood samples for analysis of venous oxygen ($P\text{v}\text{O}_2$) and carbon dioxide ($P\text{v}\text{CO}_2$) tension were taken in syringes and kept on ice until the analyses were performed 10 min later (IL 413, Instrumentation Laboratories, Italy).

### *Measurements*

For the evaluation of relative changes in capillary perfusion the amplitude obtained during undisturbed anaesthesia and before intubation of the trachea (An, see below) was chosen as reference.

E.c.g., CP, MAP and $P\text{E}'\text{CO}_2$ were measured at the following stages of anaesthesia and adenoidectomy: B = Before induction of anaesthesia; S = after induction of Sleep; An = during undisturbed Anaesthesia before intubation; Int = 1 min after Intubation; Ad = during Adenoidectomy; aAd = after Adenoidectomy; Ext = after Extubation; P = 15 min Post-op.

Blood samples were taken at stages An (sample 1), aAd (sample 2) and P (sample 3).

### *Statistics*

Comparisons between the groups were carried out with paired Student's *t* test and the Chi-square test.

## RESULTS

### *Sedative effects*

The evaluation of the sedative effects showed that the scores (table I) were greater in group B than in group A (table II). However, these differences were not significant.

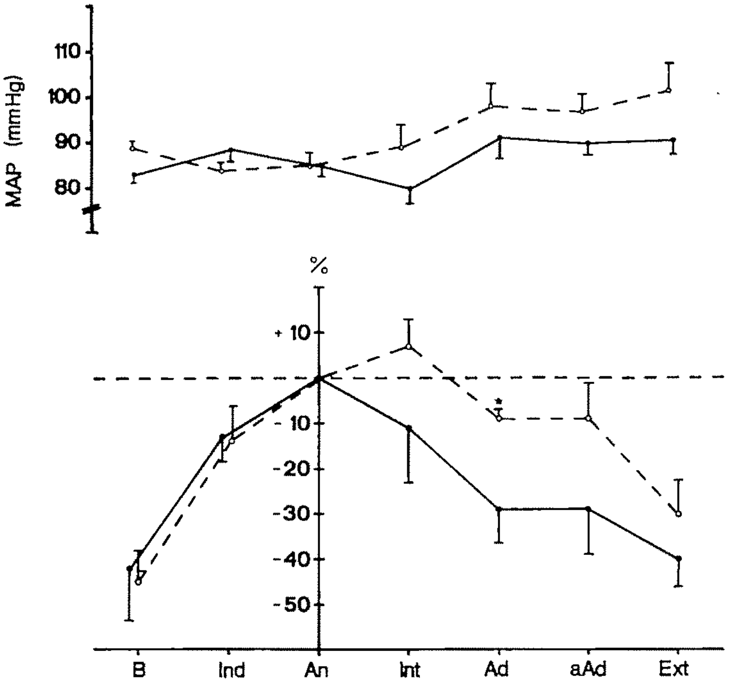

FIG. 1. Upper panel: Mean values ± SEM for mean arterial pressure (MAP). Lower panel: Mean values ± SEM for capillary perfusion during anaesthesia and adenoidectomy as related to the values at undisturbed anaesthesia (An). Group A (O—O), group B (●——●).

TABLE II. *Evaluation of sedation*

| | | | | | | | | | Summary |
|---|---|---|---|---|---|---|---|---|---|
| A | Sedation | 3 | 4 | 4 | 3 | 3 | 3 | 4 | 3.4 |
| | Antisialagogue effect | – | 0 | 0 | 0 | 0 | – | – | 3– |
| B | Sedation | 4 | 3 | 5 | 5 | 2 | 5 | 4 | 4.1 |
| | Antisialagogue effect | 0 | 0 | 0 | 0 | 0 | 0 | – | 1– |

### *Heart rate, mean arterial pressure, capillary perfusion and cardiac arrhythmias*

In both groups HR increased by about 30% during the procedure. MAP and CP were somewhat lower in group B after anaesthesia than in group A (fig. 1). At Ad capillary perfusion was significantly greater in group A than in group B ($P < 0.05$). Four children in each group had supraventricular cardiac arrhythmia. In group A, three children also developed ventricular arrhythmia, while none was seen in group B.

### *ACTH*

Plasma concentrations of ACTH at An and P were significantly less in group B than in group A ($P < 0.01$ and $P < 0.001$, respectively, fig. 2). The

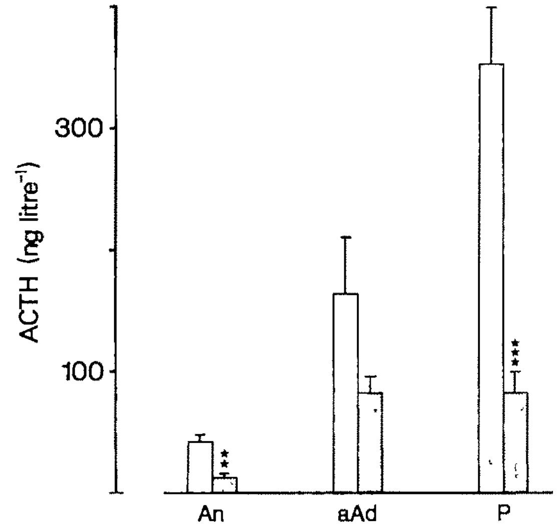

FIG. 2. Mean values ± SEM for plasma concentrations of ACTH at An, aAd and P for group A (white columns) and for group B (stippled columns). $^{**}P < 0.01$, $^{***}P < 0.001$.

values (mean ± SEM) in group A increased from 40.7 ± 6.5 ng litre$^{-1}$ at An to 352.9 ± 46.5 ng litre$^{-1}$ at P ($P<0.001$). The corresponding increase in group B was from 12.1 ± 2.0 ng litre$^{-1}$ to 82.1 ± 17.3 ng litre$^{-1}$ ($P<0.01$).

### *Cortisol*

Plasma cortisol concentrations were significantly lower in group B compared with group A ($P<0.01$, $P<0.001$ and $P<0.01$, respectively, fig. 3). The values (mean ± SEM) in group A increased from 235.7 ± 36.1 nmol litre$^{-1}$ at An to 655.7 ± 18.4 nmol litre$^{-1}$ at P ($P<0.001$). In group B the corresponding increase was from 121.4 ± 15.2 nmol litre$^{-1}$ to 427.9 ± 63.3 nmol litre$^{-1}$ ($P<0.01$).

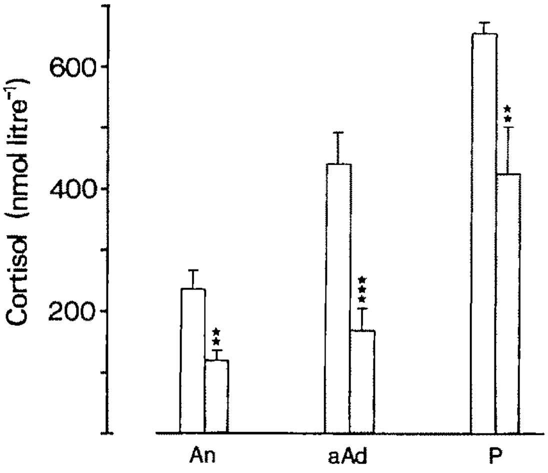

FIG. 3. Mean values ± SEM for plasma concentrations of cortisol at An, aAd and P for group A (white columns) and for group B (stippled columns). $^{**}P<0.01$ and $^{***}P<0.001$.

### *Gas exchange*

There was a statistically significant increase in respiratory rate and $PE'_{CO_2}$ in both groups during anaesthesia and surgery, but there were no significant differences between the groups (fig. 4). Venous oxygen and carbon dioxide tensions were normal in both groups.

## DISCUSSION

To avoid the diurnal variations in ACTH and plasma cortisol concentrations (Nilsson, Arner and Hedner, 1963) all children were investigated between 8.30 and 10.30 am. In both groups premedication was administered between 20 and 40 min before the induction of anaesthesia. Standardized methods for anaesthesia and surgery were used. Mean age, body weight and preoperative fasting were comparable in the two groups.

The anaesthetist judged the sedative and antisialagogue effect of the premedication used in group B to be somewhat better than in group A. The material is, however, too small for any conclusions to be drawn on sedative effects, but the results confirm earlier reports that the combination of diazepam, morphine and hyoscine is advantageous (Lindahl, Olsson and Thomson, 1981).

Surgical procedures result in an increase in plasma cortisol concentration (Sandberg, Eik-Nes and Samuels, 1954; Cooper and Nelson, 1962; Hume, Bell and Barter, 1962; Nilsson, Arner and Hedner, 1963) and the secretion of ACTH increases rapidly after the skin incision (Ichikawa et al., 1971), which is relevant in this study since the time between the first and second blood samples was only 5–10 min. In other words, ACTH and cortisol are suitable indices of the endocrine stress response during short

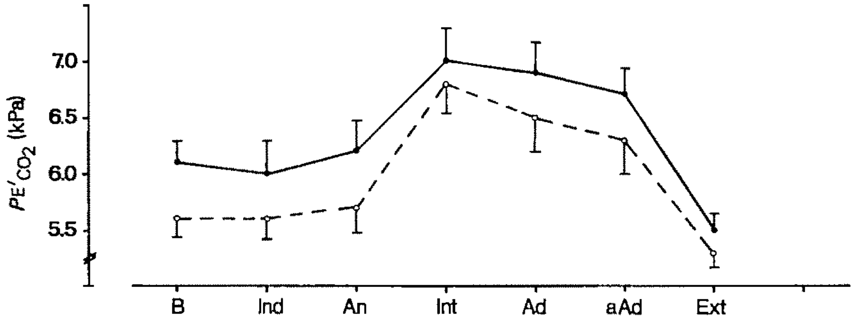

FIG. 4. End-tidal carbon dioxide tensions ($PE'_{CO_2}$, kPa) for group A (dotted line) and for group B (continues line). Mean values ± SEM.

procedures like adenoidectomy. The method used for the analysis of ACTH is known to give spurious values outside the normal range in about 2% of measurements (Hedner, Nordén and Valdemarsson, 1981). Obviously increased values were not observed in the unstressed state in the present clinical material.

It is also known that ACTH often reaches plasma concentrations above the concentration required for maximal corticosteroid output from the adrenals (Ganong, Alpert and Lee, 1974). Simultaneous analyses of plasma concentrations of ACTH and cortisol revealed a discrepancy in relative changes of plasma concentrations between ACTH and cortisol. ACTH concentrations increased more than eight times the initial value in group A, while the corresponding cortisol plasma concentrations increased less than three-fold. This supports the findings of Ganong, Alpert and Lee (1974), and demonstrates the inability of the adrenals to respond to the full ACTH stimulus.

Plasma concentrations of ACTH and cortisol were both significantly smaller in group B compared with group A, a result which, to some extent, might be explained by a decrease in anxiety. It was shown that, compared with the initial values of ACTH and cortisol during undisturbed anaesthesia, the increase after surgery was greater in group A than in group B. This cannot be explained by a decrease in anxiety alone. The suppressed ACTH and cortisol responses found in group B (premedicated with diazepam, morphine and hyoscine) might be a result of the morphine. However, the doses of morphine were small compared with those (1–4 mg kg$^{-1}$), described previously to block the ACTH and cortisol responses to surgery and stress (Reier, George and Kilman, 1973; George et al., 1974; Brandt et al., 1978).

The effect of diazepam in decreasing anxiety before operation is well documented (Tornetta, 1965; Dobkin et al., 1970) and Oyama and colleagues (1969) found that diazepam 0.2 mg kg$^{-1}$ decreased the plasma free cortisol concentration. However, the sedative effect of diazepam is dose-dependent, even though there are great individual variations in the response to the drug (Brown and Dundee, 1968). Therefore, the differences in hormonal stress response between the two groups might to a large extent be explained by the larger dose of diazepam used in group B.

In addition, it has been shown that diazepam increases the effects of pethidine, morphine and hyoscine when used in various combinations (Dundee et al., 1970). We feel that these additive effects were most probably the explanation of the clearcut differences in endocrine stress response demonstrated in this study.

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## REFERENCES

Barker, R. A., and Nisbet, H. I. A. (1973.) The objective measurement of sedation in children, a modified scoring system. *Can. Anaesth. Soc. J.*, 5, 599.

Baselius, L., and Nordström, L. (1971). A new system for routine patient monitoring. *Acta Anaesthesiol. Scand.*, (Suppl.) **XLI**.

Brandt, M. R., Korshin, J., Prange Hansen, A., Hummer, L., Nistrup Madsen, S., Rygg, I., and Kehlet, H. (1978). Influence of morphine anaesthesia on the endocrine–metabolic response to open-heart surgery. *Acta Anaesthesiol. Scand.*, 22, 400.

Brown, S. S., and Dundee, J. W. (1968). Clinical studies of induction agents. XXV: Diazepam. *Br. J. Anaesth.*, 40, 108.

Cooper, C. E., and Nelson, D. H. (1962). ACTH levels in plasma in preoperative and surgically stressed patients. *J. Clin. Invest.*, 41, 1599.

Dobkin, A. B., Israel, J. S., Evers, W., and Bisset, C. M. (1970). Double-blind evaluation of diazepam for premedication. *Can. Anaesth. Soc. J.*, 17, 52.

Dundee, J. W., Haslett, W. H. K., Keilty, S. R., and Pandit, S. K. (1970). Studies of drugs given before anaesthesia. XX: Diazepam-containing mixtures. *Br. J. Anaesth.*, 42, 143.

Engqvist, A., Brandt, M. R., Fernandes, A., and Kehlet, H. (1977). The blocking effect of epidural analgesia on the adrenocortical and hyperglycemic response to surgery. *Acta Anaesthesiol. Scand.*, 21, 330.

Ganong, W. F., Alpert, L. C., and Lee, T. D. (1974). ACTH and the regulation of adrenocortical secretion. *N. Engl. J. Med.*, 290, 1006.

George, J. M., Reier, C. E., Lanese, R. R., and Rower, M. (1974). Morphine anesthesia blocks cortisol and growth hormone response to surgical stress in humans. *J. Clin. Endocrinol.*, 38, 736.

Hall, G. M., Young, C., Holdcroft, A., and Alaghband-Zadeh, J. (1978). Substrate mobilization during surgery: A comparison between halothane and fentanyl anaesthesia. *Anaesthesia*, 33, 924.

Hedner, P., Nordén, N. E., and Valdemarsson, S. (1981). Falsely high values for corticotrophin by the CIS-Sorin RIA method. *Clin. Chem.*, 27, 1146.

Hume, D. M., Bell, C. C., and Barter, F. (1962). Direct measurement of adrenal secretion during operative trauma and convalescence. *Surgery*, 52, 174.

Ichikawa, Y., Kawagoe, M., Nishikai, M., Yoshida, K., and Homma, M. (1971). Plasma corticotrophin (ACTH), growth hormone (GH) and 11-OHCS (hydroxycorticosteroid) response during surgery. *J. Lab. Clinical. Med.*, 78, 882.

Lindahl, S., Olsson, A.-K., and Thomson, D. (1981). Rectal premedication in children. Use of diazepam, morphine and hyoscine. *Anaesthesia*, 36, 376.

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# A MOBILE INTENSIVE CARE UNIT* BASED ON A STANDARD AMBULANCE TROLLEY BED

G. R. PARK, S. JOHNSON, A. FERGUSON AND D. GRANT

## SUMMARY

An inexpensive, versatile Mobile Intensive Care Unit is described. By designing the unit around a standard ambulance trolley no running costs are incurred in the maintenance of a purpose-built unit based on an ambulance used purely for this purpose. The equipment is portable and compact and can be transported by any available means, including a taxi, to the referring hospital. Only when the patient is ready for transfer is an ambulance asked for, making the minimum use of emergency ambulance time. It contains all the equipment necessary to monitor and ventilate artificially a critically ill patient during transfer and all the drugs and disposables to treat any emergencies that may arise in this period.

The movement of critically ill patients between hospitals has been shown to be hazardous (Waddell et al., 1975; Hotherall et al., 1977). Moving such patients may be required either for further treatment, such as transfer to a regional intensive care unit, or for specialist investigations, such as computerized axial tomography. Because of the risks thought to exist, patients either are not transferred, denying them specialist treatment or investigation, or if they are transferred it is often unnecessarily rapid. During a rapid transfer inadequate monitoring, treatment and supervision may occur. The feasibility and advantages of a mobile intensive care unit (MICU) have been well described by the Glasgow Shock Study Group (Waddell et al., 1975; Hothersall et al., 1977). An extension of this original concept led to the development in Oxford (Aitkenhead, Willis and Barnes, 1980) of a more economical unit based on an ambulance no longer required by the Ambulance Service. Both of these units are ideal for transferring critically ill patients.

It was decided to establish transport facilities for the Assisted Ventilation Unit (AVU) at the Royal Infirmary, Edinburgh. The AVU accepts patients referred to it who require ventilation or intensive monitoring. Patients are transferred from hospitals in Edinburgh, South Fife, and the Eastern Borders, involving distances of up to 30 miles. The number of patients is much smaller than in Glasgow or Oxford, averaging one transfer per month to the AVU. It is difficult to justify both the initial expense and maintenance costs or the use of valuable, secure, dry storage space for a purpose-adapted ambulance.

The time taken to stabilize a patient for transfer and for a lengthy return journey could be several hours. The Scottish Ambulance Service (SAS) are unable to provide an ordinary ambulance and crew, especially at night when only three ambulances are available for the City, for the prolonged period necessary. A modified hospital trolley (Aitkenhead, Willis and Barnes, 1980) could not therefore be used since no means existed of transferring it to the referring hospital.

We needed a MICU that was:

(1) cheap to produce and maintain;
(2) portable;
(3) easy to use;
(4) compatible with existing AVU equipment.

We devised a frame that could be clipped on to a standard ambulance trolley and equipped it with a drug box, three cases of apparatus, monitors and an airbed.

### *Ambulance trolley frame*

The frame is L-shaped with a spring-loaded clamp at one end. It is clipped on to a standard ambulance trolley bed and converts it into a self-contained MICU (fig. 1). When not clipped to the ambulance trolley it is used as a carrier for the rest of the equipment in a manner similar to a supermarket trolley (fig. 2). It is constructed of square-section chromium-plated steel frame with a milled aluminium clamp. The spring loaded upper and

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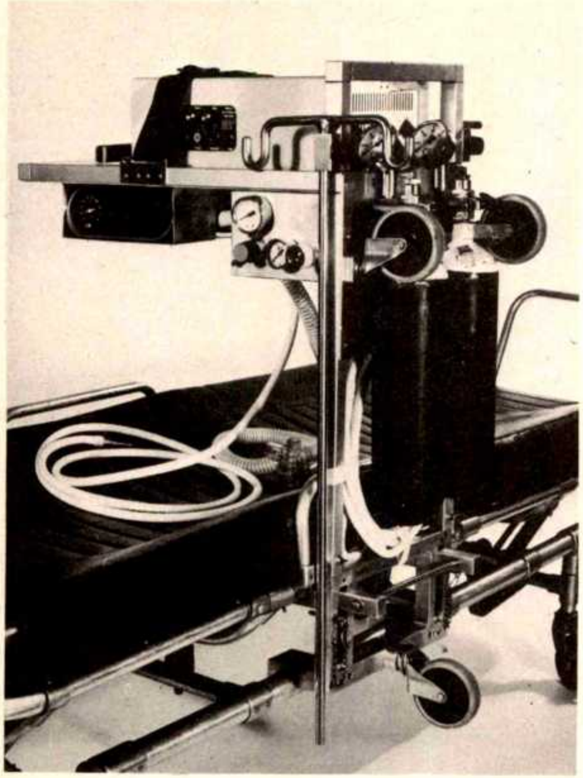

FIG. 1. Standard ambulance trolley bed with the ambulance trolley frame in position.

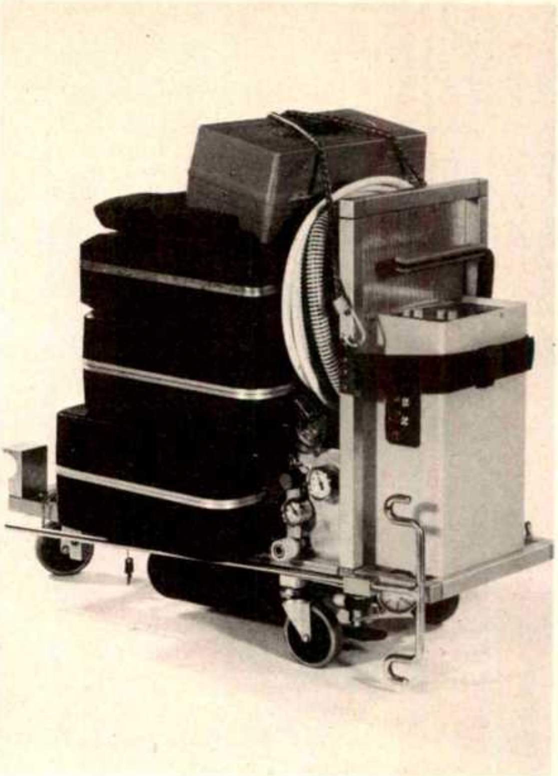

FIG. 2. Ambulance trolley frame and equipment packed for transport to the referring hospital.

lower jaws of the clamp fit on to the longitudinal members of the bed. Safety pins prevent accidental dislodgement (figs 1,3). Two sets of lower jaws are available which enable it to be fitted to most types of ambulance trolley beds in this region. The side of the frame (fig. 4) carries two size D oxygen cylinders, their yokes and pressure gauges, extendable dripstand, two fixed wheels and one steerable wheel. The oxygen cylinders are connected through reducing valves to a 60 $\mathrm{lbf\,in^{-2}}$ Schrader outlet which is used to drive the ventilator and to a Bourdon type oxygen flow gauge (Oxylitre (Edinburgh) Ltd). These devices can also be fed through a 1.5-m length of high pressure flexible tubing and one-way valve allowing the larger oxygen cylinder in the ambulance to be used. All of the fixed pipework and reducing valves are contained in a compartment under the shelf to prevent damage (fig. 1). Further along the shelf is a housing for the fluid logic ventilator. Small lugs are built into either side of the shelf to enable a retaining strap for the monitor and cases to be fitted. The frame is small enough to fit, complete with equipment, into the luggage space of a standard Austin taxi.

*Equipment used with the frame*

The Drager Oxylog, a recently marketed small, fluid logic ventilator is used which has several advantages over other small fluid logic ventilators designed for use in these circumstances (Harber and Lucas, 1980; Gray, 1981; Marsh and Ledingham, 1981). Most important, it can deliver 100% oxygen or entrain air which allows extended running time from oxygen cylinders. The ability to use 60% oxygen when the airmix is used will reduce absorption atelectasis caused by the use of 100% oxygen (Nunn et al., 1965; Burger and Macklem, 1968). It has an airway pressure gauge, but PEEP is not recorded because the gauge is sited on the inspiratory limb. Frequency and minute volume can be set with reasonable accuracy from the control for infant to adult values. The patient circuit can be steam-autoclaved. A fuller description and evaluation of this ventilator has been published elsewhere (Park

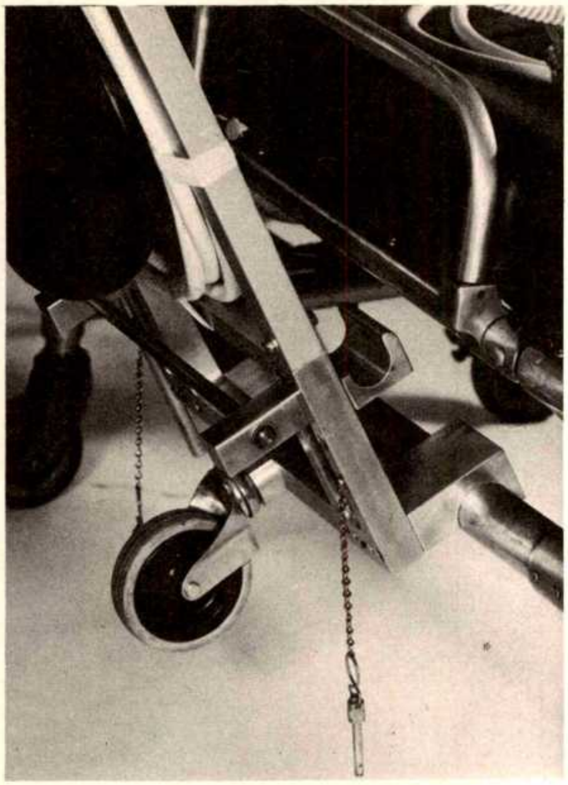

FIG. 3. Ambulance trolley frame clamp about to be locked into position on the longitudinal members of the ambulance trolley bed.

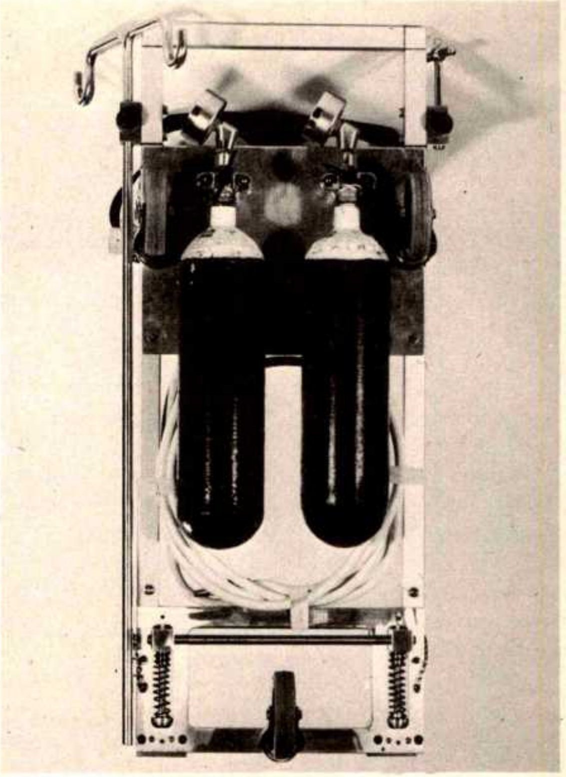

FIG. 4. Side view of ambulance trolley frame.

and Johnson, 1982). A digital display respirometer (Spirox H, East of Oxford) can be fitted on to the expiratory part to give a continuous read-out of minute or tidal volume.

The cardiovascular monitor (Statscope II; Becton – Dickinson) can be used with mains or rechargeable batteries with a life of 3.5 h. E.c.g. and pressure waveforms are displayed. Digital values of systolic, diastolic and mean arterial pressures, heart rate and temperature are also shown.

*Other equipment*

All the equipment necessary for emergencies during transport are held in three cases along with specialist equipment that may not be available in the referring hospital. In each case the equipment is packed into U-sections made from plastic rainwater guttering and sealed with transparent catering film or polythene bags to allow rapid visual checking of the contents. Drugs are held into a fishing tackle box using double-sided adhesive tape to prevent damage during transit. To avoid problems with the need for secure containers to hold controlled drugs, opiates are obtained from the referring hospital. The contents of the three cases are shown in the appendix.

An inflatable airbed is used to prevent vehicle vibrations being transmitted to the patient. If necessary it can be rapidly deflated. A washable synthetic sleeping bag is available for use in cold weather.

Suction is not fitted to the frame or carried in the cases because all emergency ambulances in this region carry battery- and foot-powered suction units. If this facility is not available, a small gas-powered suction unit (Laerdal) could easily be fitted to the frame or carried in one of the cases. A defibrillator is not routinely carried. Attention to adequate resuscitation and oxygenation before and during transfer should render one almost unnecessary (I.McA. Ledingham, personal communication).

*Practical considerations*

When a request is made for the MICU, a suitably experienced senior registrar (from either the AVU or the emergency team) and nurse collect the equipment and travel to the referring hospital. Up to now taxi transport to the referring hospital has been adequate, but should it be required more urgently then the SAS or Police have agreed to undertake transport. When the patient's condition has been stabilized (which may take some time) the local ambulance control is asked to send an ambulance which can be converted to its MICU role in approximately 10 min. The ambulance trolley bed is taken to the patient's bedside where the patient and the frame are put on the bed and the patient is then transferred. This reduces to a minimum the time during which the ambulance is unavailable for other emergency duties. The patient is usually transferred in the ambulance head-first on the nearside of the vehicle. Because calls are infrequent no formal on-call team exists; however, a group of three senior registrars have agreed to undertake or advise on transfers. A small nucleus thus exists for future developments, maintenance of equipment, and teaching.

The equipment used with the frame is also used on a bed-mounted unit which is used when critically ill patients are moved around the hospital (Park and Johnson, 1981). This enables familiarity with the equipment to be obtained and maintained.

Use of a standard ambulance trolley in its usual position (fig. 5) means that access to the right side of the patient is limited, neither can the trolley be tipped head-down. Neither of these limitations has proved a problem if the patient is adequately resuscitated before transfer. There is good access to the head if the seat at the top of the trolley bed is folded up. The lighting in a standard ambulance is satisfactory and a portable spotlight running off the vehicle power supply is available should any procedures be necessary.

## DISCUSSION

This system is inexpensive, portable and versatile. It has proved satisfactory in use for transferring patients to an AVU from a referring hopistal. Ambulance facilities are used for the minimum period of time. If urgency regularly exists over transfer of patients, such as those with head injuries, from a district general hospital to a regional hospital, a similar unit could be held and used by the referring hospital. Gentleman and Jennet (1981) have shown that considerable morbidity occurs when these patients are transferred; paralysis and ventilation has been suggested (Price, 1981) as a means of overcoming this. The use of a unit such as the one described should make transfer of these patients safer.

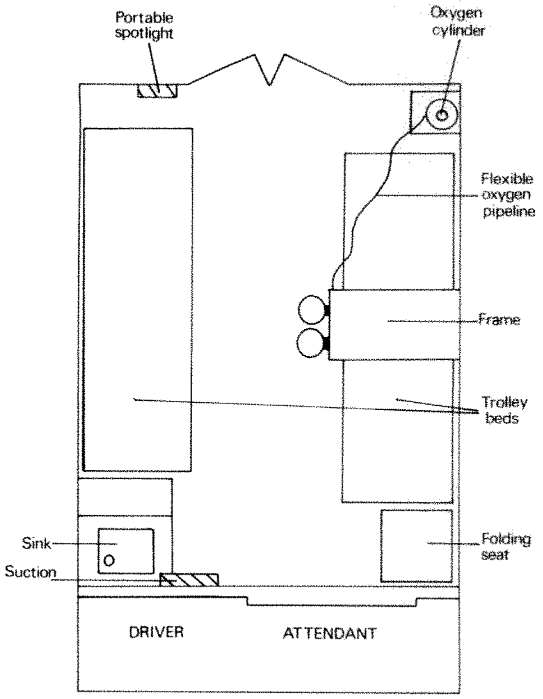

FIG. 5. Interior plan (not to scale) of a Bedford ambulance adapted for mobile intensive care.

By basing the MICU on a standard ambulance trolley, it has proved extremely versatile. The helicopter currently in service with the Royal Air Force Search and Rescue Units (Wessex Mk III) will accept this unit, which should considerably ease loading and unloading. By train, we have transferred from Edinburgh to London a patient who required continuous pulmonary ventilation throughout the journey. Use of this unit enabled a guard's compartment in a high-speed train to be used instead of an aircraft, with avoidance of a steep head-up and -down tilt during take-off and landing, with little difference in the time taken for transfer and a large saving in cost. Once the patient was moved on to the ambulance trolley in Edinburgh she did not require to be moved off it again until she was in hospital in London.

## APPENDIX

### DETAILS OF CONTENTS OF THE CASES

*Case 1—"Disposables"*

2 chest drain sets

1 i.v. set containing assorted cannulae, blood filters, etc.

1 dressing set containing bandage, adhesive tape, sutures, etc.
1 multivent oxygen mask
1 400 ml of purified protein fraction
1 500 ml of 5% dextrose
1 500 ml of 0.9% saline
1 200 ml of 8.4% sodium bicarbonate
1 metallized plastic blanket
Suction catheters, Coude, Straight, etc.
1 drip regulator (Dial-o-Flow)

*Case 2—"Airway"*
1 self-inflating bag and face-masks
Assorted oro-pharyngeal airways
Assorted endotracheal tubes — red rubber and plastic
Laryngoscope
Intubating accessories (introducer, lubricating jelly, etc.)
Cricothyroid membrane puncture needle
Reducing valve to adapt large ambulance oxygen cylinders to our needs

*Case 3—"Monitoring"*
Stethoscope
Aneroid sphygmomanometer
Tape measure
Arterial line equipment
Torch
Digital display respirometer (Spirox H)
Instruction manuals, check lists, paper and charts

### ACKNOWLEDGEMENTS

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The frame and associated equipment is manufactured and can be supplied by Oxylitre (Edinburgh) Ltd, Riverside Works, Miller Row, Edinburgh EH4 3BQ.

### REFERENCES

Aitkenhead, A. R., Willis, M. I., and Barnes, W. M. (1980). An economical mobile intensive care unit. *Br. Med. J.*, **280**, 1219.

Burger, E. J., and Macklem, P. (1968). Airway closure: demonstration by breathing 100% oxygen at low lung volumes and by nitrogen washout. *J. Appl. Physiol.*, 27, 191.

Gentleman, D., and Jennet, B. (1981). Hazards of interhospital transfer of comatose head-injured patients. *Lancet*, 2, 853.

Gray, A. J. G. (1981). Portable lung ventilators. *Br. J. Hosp. Med.*, **25**, 173.

Harber, T., and Lucas, B. G. B. (1980). Mechanical resuscitators for use in the ambulance service. *Ann. R. Coll. Surg. Eng.*, 62, 291.

Hothersall, A. P., Waddell, G., Smith, H. C., Gilmour, D. G., Ledingham, I.McA; Green, M. L., and Weller, G. (1977). Mobile intensive care II—secondary transport; in *Recent Advances in Intensive Therapy*, chapter 18. Edinburgh: Churchill Livingstone.

Marsh, R. M. K., and Ledingham, I.McA. (1981). Equipment for mobile intensive care. *Br. J. Hosp. Med.*, 25, 377.

Nunn, J. F., Coleman, A. J., Sachithranan, T., Bergam, N. A., and Lewis, J. W. (1965). Hypoxaemia and atelectasis produced by forced expiration. *Br. J. Anaesth.*, 37, 3.

Park, G. R., and Johnson, S. (1981). A bed-mounted unit for the movement of critically ill patients. *Anaesthesia*, 36, 624.

Park, G. R., and Johnson, S. (1982). A ventilator for use during mobile intensive care and total intravenous anaesthesia. *Anaesthesia*, (in press).

Price, D. G. (1981). Transferring the comatose head-injured patient. *Lancet*, 2, 985.

Waddell, G., Scott, P. D. R., Less, N. W., and Ledingham, I. McA. (1975). Effects of ambulance transport in critically ill patients. *Br. Med. J.*, 1, 386.

## EINE MOBILE INTENSIVPFLEGEEINHEIT, DIE AUF EINEM STANDARD-KRANKENWAGEN AUFGEBAUT IST

### ZUSAMMENFASSUNG

Es wird eine preisgünstige, vielseitige mobile Intensivpflegeeinheit beschrieben. Dadurch, daß die Einheit auf einem Standard Rettungswagen aufgebaut ist, treten keine Kosten für die Erhaltung eines Fahrzeuges auf, das ausschließlich für diesen einzigen Zweck konstruiert ist. Die Ausrüstung ist tragbar und handlich und kann auf jede Weise, einschließlich eines Taxis zum entsprechenden Krankenhaus transportiert werden. Erst wenn der Patient transportfähig ist, wird der Krankenwagen gerufen, wodurch die Inanspruchnahme eines Rettungswagens so klein wie möglich gehalten wird. Sie enthält die zur Öberwachung und künstlichen Beatmung eines Schwerkranken auf dem Transport notwendigen Instrumente, sowie alle Medikamente und Artikel zur Behandlung jedes in dieser Periode auftretenden.

## UNIDAD MOVIL DE CUIDADOS INTENSIVOS BASADA EN UNA CAMA DE RUEDAS TIPICA DE AMBULANCIAS

### SUMARIO

Se describe una unidad móvil para cuidados intensivos que es versátil y económica. Al diseñar la unidad en base a una camilla de ruedas de las usadas en ambulancias no se crean los costes de mantenimiento que existirían en la gestión de una unidad construida ex profeso, a usar en una ambulancia dedicada sóla y exclusivamente para estos fines. El equipo y portátil y de tamaño reducido y puede transportarse en los medios de que se disponga, incluyendo un taxi, hasta el hospital pertinente. Sólo se solicita una ambulancia cuando el paciente se encuentra ya listo para su traslado, lo que implica el mínimo uso del tiempo de emergencia de las ambulancias. Dicha unidad contiene todo el equipo necesario para vigilar y ventilar artificialmente a un paciente en condiciones críticas durante el traslado y todas las drogas y elementos de uso único que son necesarios para tratar toda emergencia que pueda surgir durante este periodo de tiempo.

*Br. J. Anaesth.* (1982), 54, 1087

# PLASMA FENTANYL CONCENTRATIONS AND THE OCCURRENCE OF RESPIRATORY DEPRESSION IN VOLUNTEERS

H. STOECKEL, J. SCHÜTTLER, H. MAGNUSSEN AND J. H. HENGSTMANN

## SUMMARY

Healthy volunteers received single doses of fentanyl 0.5 mg i.v. and the occurrence of respiratory depression was correlated with secondary peaks in the plasma concentrations of fentanyl. Plasma concentrations of fentanyl, tidal volume, minute volume, end-tidal $P_{CO_2}$, arterial blood-gas tensions, and response curves to carbon dioxide were determined during the total study period of 240 min. Secondary increases in the plasma concentrations of fentanyl occurred in four of the seven volunteers. These four individuals showed marked depression of their carbon dioxide response curves and in two respiratory insufficiency was evident clinically.

Several studies attest to the dose-related respiratory depression induced by a single bolus injection of fentanyl (Downes, Kemp and Lambertsen, 1967; Harper et al., 1976; Kaufmann, Aqleh and Bellville, 1979; Rigg and Goldsmith, 1976). In addition, Becker and colleagues (1976) noted the occurrence of bisphasic respiratory depression when either fentanyl alone, or fentanyl plus droperidol, were used as a supplement to nitrous oxide anaesthesia. Adams and Pybus (1978) observed delayed respiratory depression in three patients after apparent recovery from general anaesthesia produced by fentanyl. These cases of delayed respiratory depression were successfully treated with naloxone. McQuay and colleagues (1979), Stoeckel, Hengstmann and Schüttler (1979), Fung and Eisele (1980) and McClain and Hug (1980) have all reported secondary peaks when measuring plasma concentrations of fentanyl. Although it has been shown that the disposition of fentanyl can be altered with secondary increases in its plasma concentrations after a bolus injection, the frequency, magnitude and temporal sequence of this phenomenon (Cascorbi and Gravenstein, 1974) are unclear. The present study addressed this question by determining the plasma concentrations of fentanyl at various time intervals and correlating these with measurements of respiratory variables, arterial blood-gas tensions and carbon dioxide responsiveness.

## SUBJECTS AND METHODS

Seven healthy adult volunteers (three male), were selected for this study following a detailed medical examination. Written informed consent was obtained after each volunteer had received a report summarizing the pharmacodynamic effects of fentanyl, the purpose and the potential hazards of the investigation. The general characteristics of the subjects are presented in table I.

The experiments were performed at least 4 h after the last meal.

Each volunteer received a bolus injection of fen-

TABLE I. *General characteristics of volunteers.*
$^{*}wt^{0.425} \times ht^{0.725} \times 71.84$

| Volunteer | Sex | Age (yr) | Wt (kg) | Ht (cm) | Body surface area* ($m^2$) |
|---|---|---|---|---|---|
| 1 | M | 20 | 62 | 175 | 1.76 |
| 2 | F | 22 | 60 | 176 | 1.74 |
| 3 | F | 34 | 50 | 155 | 1.47 |
| 4 | M | 35 | 63 | 172 | 1.75 |
| 5 | F | 26 | 58 | 167 | 1.65 |
| 6 | M | 21 | 77 | 185 | 2.00 |
| 7 | F | 26 | 59 | 172 | 1.70 |
| Group I | | | | | |
| (Volunteers 1, 6, 7) | | | | | |
| Mean | | 22.3 | 66.0 | 177.3 | 1.820 |
| SEM | | ±3.2 | ±9.6 | ±6.8 | ±0.159 |
| Group II | | | | | |
| (Volunteers 2, 3, 4, 5) | | | | | |
| Mean | | 29.3 | 57.8 | 167.5 | 1.653 |
| SEM | | ±6.3 | ±5.6 | ±9.1 | ±0.130 |

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tanyl 0.5 mg in a forearm vein. Venous blood was sampled from the opposite forearm at 2, 5, 10, 15, 30, 45, 60, 75, 90, 105, 180, 210 and 240 min following injection. Measurements of fentanyl in plasma were performed by radioimmunoassay (Michiels, Hendriks and Heykants, 1977). Coefficient of variation was ±5% for a concentration of 1 μg litre$^{-1}$ (0.97 ± 0.05 μg litre$^{-1}$) and ±10.2% for a 5-μg litre$^{-1}$ sample. Although commercially available fentanyl (as the citrate salt) was administered, the dose and concentrations in this paper refer to the free base. The ventilatory response to carbon dioxide was measured as described by Read (1967). The subjects rebreathed from a 5-litre bag filled with 7.5% carbon dioxide plus oxygen. The bag was fitted in an air-tight plastic box. Volume changes within the box were measured by means of the integrated signal from a Fleisch pneumotachograph.

End-tidal $P_{CO_2}$ was measured continuously using an infra-red analyser (URAS, Hartmann & Braun, West Germany). Gas was sampled at the mouthpiece and returned to the bag. The average minute ventilation and end-tidal $P_{CO_2}$ were calculated for a 20-s period and produced 12 data points during the total rebreathing time of 4 min. These values were used to calculate the carbon dioxide response $\Delta\dot{V}_E/\Delta P_{E_{CO_2}}$ slopes by least square linear regression analysis. To prepare the subjects, two ventilatory responses were undertaken 60 and 30 min before the injection of fentanyl and the mean of these two slopes was accepted as the control value. Carbon dioxide response curves were repeated 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210 and 240 min following the injection of fentanyl. The change in slope of the carbon dioxide response curves was used to evaluate the respiratory depressant effect of fentanyl because the range of set-point values after the injection of fentanyl was smaller when compared with the slope values and the differences between subjects of the baseline set points were greater. The carbon dioxide response tests were performed almost simultaneously with the sampling for measurement of the blood concentrations. Between these measurements, minute volume, tidal volume, respiratory rate, and end-tidal $P_{CO_2}$ were measured continuously from 30 min before the injection of fentanyl to 240 min after the injection by allowing the subject to breathe through a rubber mask connected to a Fleisch No. 3 pneumotachograph. Oxygen and carbon dioxide partial pressures were measured in blood samples from hyperaemic ear lobes. Blood-gas and pH measurements were performed using standard electrodes calculated with two gas mixtures. Arterial pressure (Riva Rocci method) was measured every 5 min for the first 30 min and every 15 min for the remaining period. The electrocardiogram was monitored continuously. During each study equipment was available for cardiopulmonary resuscitation, and artificial ventilation could be given from an anaesthetic machine if necessary.

## RESULTS

The administration of a bolus of fentanyl 0.5 mg i.v. produced primary respiratory depression, with changes in the responsiveness to carbon dioxide in all of the volunteers although the degree of depression varied between subjects. Three of the volunteers became apnoeic for a brief period and required artificial ventilation with oxygen via a face mask for 2–7 min. Four subjects fell asleep for 5 min immediately after the injection, but this had no effect on the evaluation of their carbon dioxide response. The slopes of the carbon dioxide response curves were depressed in all of the subjects such that the set point of the curves revealed a marked shift to the right. Initially, the plasma concentrations of fentanyl showed a biphasic decay curve, but later a secondary increase in plasma concentrations occurred in four subjects. Corresponding to this increase there was a secondary depression of slope of the carbon dioxide response curve. Clinically, two of these particular volunteers had evidence of secondary respiratory insufficiency.

Figure 1 illustrates the plasma concentration of fentanyl (mean ± SEM), the carbon dioxide response (mean ± SEM), and the minute volume of ventilation (mean ± SEM) in those three volunteers without secondary plasma peaks. Following the injection of fentanyl 0.5 mg, the concentration decreased rapidly from 32 to 3.7 μg litre$^{-1}$. This distribution phase was followed by a slower decay representing mainly the elimination phase. The initial slope of the carbon dioxide response curve 15 min following injection was decreased to 32.3 ± 13% when compared with the control slope. This was followed by a fast recovery phase with values of approximately 65% of normal by 45 min. Later, the carbon dioxide response curve moved slowly upward, but even at 240 min after the injection was only 78.7 ± 12.1% of the control slope.

A rapid decrease in the minute volume ($\dot{V}_E$) was observed immediately following injection of fentanyl with a minimum value of 2.0 litre min$^{-1}$ ± 0.9

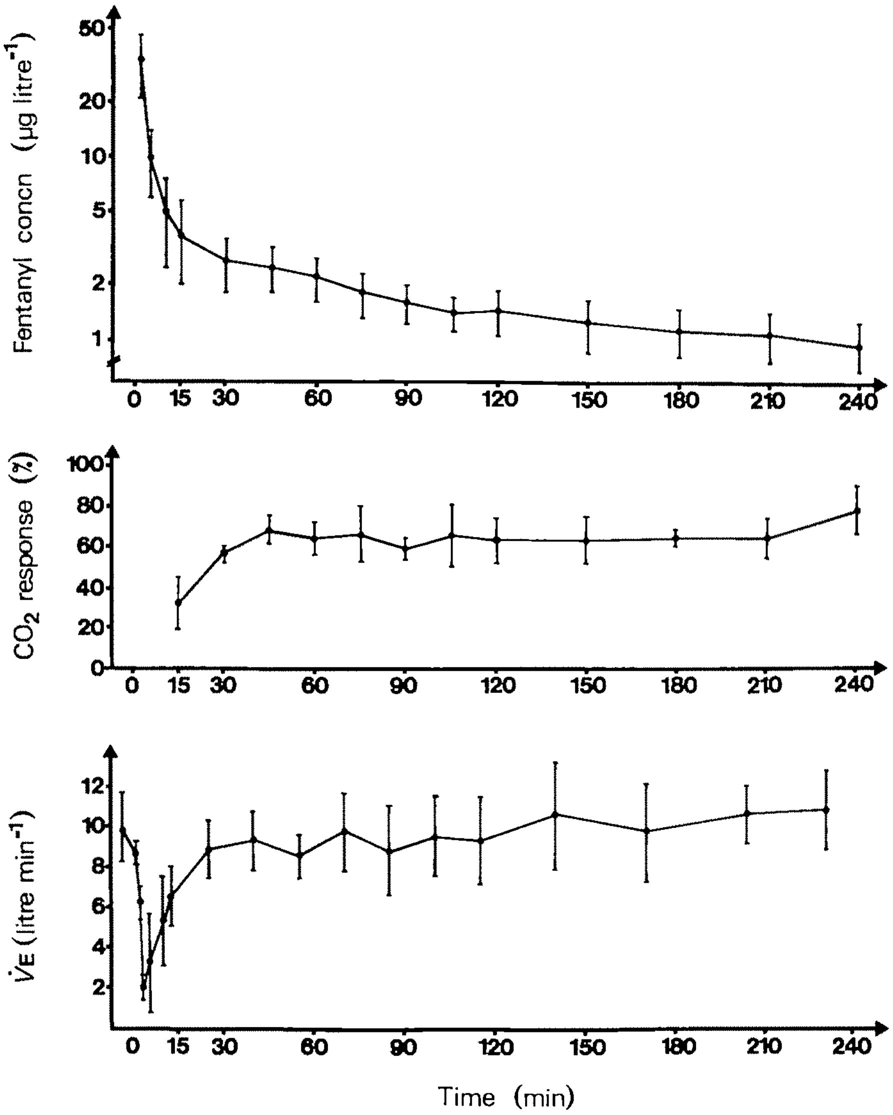

FIG. 1. Fentanyl plasma concentrations (mean ± SEM) (upper panel); carbon dioxide response slopes as percentages of the control slope (mean ± SEM) (middle panel); and minute ventilation (mean ± SEM) (lower panel), in the three volunteers without respiratory rebound phenomenon after a single bolus injection of fentanyl 0.5 mg.

after 3 min. Thereafter, there was a rapid recovery to near control values (approximately 9 litre min$^{-1}$ 25 min after injection). Thereafter, the minute ventilation remained constant. Blood-gas analysis (table II) measured in those subjects without secondary peak concentrations of fentanyl demonstrated a decrease in oxygenation for 25 min. The $Pa_{CO_2}$ and pH measurements (mean ± SEM) showed evidence of a moderate respiratory acidosis.

Fentanyl plasma concentrations, carbon dioxide response curves and $\dot{V}$E are shown in figures 2 and 3 respectively for the two volunteers who had evidence of secondary respiratory insufficiency. The secondary increases in the plasma concentrations of fentanyl were observed between 45 and 60 min. When the carbon dioxide response curve had recovered to approximately 40% of control, there was a further increase in plasma concentrations of fen-

TABLE II. *Average values of arterial blood-gas tensions in the three subjects without secondary respiratory depression (group I) (mean±SEM) and individual values for the subjects with evidence of respiratory rebound phenomena (group II)*

| | | Pre-injection control | Time after injection (min) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 10 | 25 | 55 | 85 | 115 | 140 | 170 | 230 |
| Group I | $P_{O_2}$ (kPa) | 12.6<br>±0.20 | 6.6<br>±2.85 | 11.0<br>±0.18 | 11.3<br>±0.79 | 11.5<br>±0.54 | 11.8<br>±0.50 | 11.5<br>±0.95 | 12.0<br>±0.67 | 12.2<br>±0.20 |
| | $P_{CO_2}$ (kPa) | 5.0<br>±0.51 | 6.6<br>±0.15 | 6.8<br>±0.63 | 6.0<br>±0.38 | 5.6<br>±0.51 | 5.6<br>±0.40 | 5.5<br>±0.40 | 5.2<br>±0.41 | 5.1<br>±0.08 |
| | pH (unit) | 7.43<br>±0.012 | 7.31<br>±0.046 | 7.32<br>±0.038 | 7.35<br>±0.026 | 7.37<br>±0.006 | 7.37<br>±0.025 | 7.37<br>±0.035 | 7.39<br>±0.36 | 7.40<br>±0.006 |
| Group II | | | | | | | | | | |
| Volunteer 2 | $P_{O_2}$ (kPa) | 12.3 | 6.0 | 10.3 | 7.7 | 10.5 | 10.4 | 11.3 | 10.0 | 9.9 |
| | $P_{CO_2}$ (kPa) | 5.5 | 6.5 | 4.9 | 6.5 | 6.3 | 6.3 | 6.3 | 5.6 | 6.0 |
| | pH (unit) | 7.38 | 7.32 | 7.43 | 7.30 | 7.36 | 7.37 | 7.37 | 7.38 | 7.36 |
| Volunteer 3 | $P_{O_2}$ (kPa) | 12.4 | 6.0 | 12.4 | 8.1 | 12.7 | 12.4 | 12.7 | 12.5 | 11.6 |
| | $P_{CO_2}$ (kPa) | 5.6 | 7.2 | 6.4 | 7.3 | 6.0 | 5.3 | 5.5 | 5.3 | 5.5 |
| | pH (unit) | 7.36 | 7.31 | 7.32 | 7.30 | 7.38 | 7.39 | 7.38 | 7.40 | 7.3 |
| Volunteer 4 | $P_{O_2}$ (kPa) | 12.0 | 6.4 | 13.6 | 12.3 | 14.1 | 14.1 | 13.6 | 12.8 | 12.7 |
| | $P_{CO_2}$ (kPa) | 4.9 | 6.3 | 5.1 | 5.3 | 6.3 | 5.2 | 5.1 | 5.1 | 5.5 |
| | pH (unit) | 7.48 | 7.35 | 7.42 | 7.42 | 7.38 | 7.45 | 7.42 | 7.41 | 7.40 |
| Volunteer 5 | $P_{O_2}$ (kPa) | 11.5 | — | 9.9 | 10.5 | 10.8 | 9.9 | 11.3 | 12.8 | 11.2 |
| | $P_{CO_2}$ (kPa) | 4.7 | — | 6.3 | 6.0 | 5.7 | 6.0 | 5.5 | 4.7 | 5.1 |
| | pH (unit) | 7.42 | — | 7.31 | 7.31 | 7.32 | 7.29 | 7.34 | 7.41 | 7.39 |

tanyl and secondary depression of the carbon dioxide response curves to 0 and 20% respectively. After this the recovery phase was not different from the group of individuals who did not demonstrate secondary peak plasma concentrations. The initial decrease of $\dot{V}_E$ was of similar magnitude to the other volunteers. However, during the secondary increases in plasma concentration, there were decreases in $\dot{V}_E$ with values of 1.6 litre min$^{-1}$ and 2.4 litre min$^{-1}$ respectively. Blood-gas analyses for these two subjects (table II) demonstrated initial values similar to the three subjects described previously. However, 55 min after the injection of fentanyl, secondary respiration insufficiency was manifest by decreases in $P_{aO_2}$, increases in $P_{aCO_2}$, and decreases in pH values. The secondary increases in plasma fentanyl concentrations were, however, not always followed by clinically important respiratory depression. This is noted in figures 4 and 5. Although the carbon dioxide response curve was depressed slightly in association with increases in plasma fentanyl concentrations, the effect was not sufficiently great to produce any alteration in $\dot{V}_E$ or blood-gas tensions.

## DISCUSSION

The clinical relevance of the biphasic course of respiratory depression after the administration of opioids such as fentanyl is determined by the frequency of the fentanyl rebound phenomenon, the onset of the maximum second plasma peaks and the magnitude of respiratory insufficiency. Additional factors, not relevant to this study because of the use of healthy young volunteers, could be operating in surgical patients. These include alterations in circulatory variables affecting the pharmacokinetic disposition of fentanyl, the presence of respiratory disease, and changes in organ blood flow secondary to surgery and anaesthesia. Interactions with other drugs used to supplement anaesthesia could be involved also. In addition to the marked primary respiratory depression, we observed, in four of our subjects, a secondary plasma peak which was temporally related to a decrease of the carbon dioxide response curve (fig 2–5). In two subjects secondary respiratory depression of clinical significance occurred ($\dot{V}_E$: 1.6 litre min$^{-1}$ and 2.4 litre min$^{-1}$). The duration of these periods of respiratory depression was approximately 20–30 min. The clinical

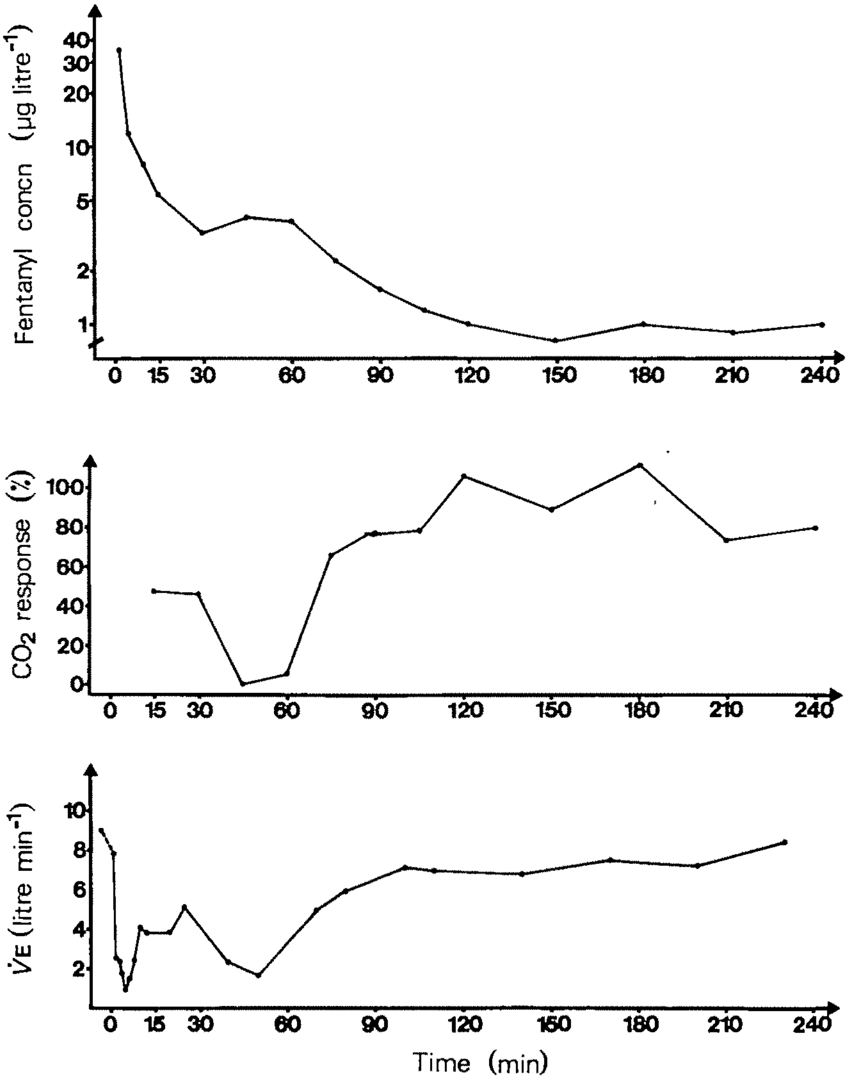

FIG. 2. Fentanyl plasma concentrations (upper panel); carbon dioxide response slopes as percentages of the control slope (middle panel); and minute ventilation (lower panel) in a volunteer (no. 2) with secondary respiratory depression after a single bolus injection of fentanyl 0.5 mg.

importance of this phenomenon was underlined by the associated decreases in $P_{aO_2}$ and increases in $P_{aCO_2}$ (table II). Thus there was a correlation between the secondary depression of the carbon dioxide response curve and secondary respiratory insufficiency and the second peak of plasma fentanyl concentrations.

Becker and co-workers (1976) observed that 90% of the patients they investigated demonstrated bisphasic respiratory depression following the injection of fentanyl. However, in their studies several other factors (surgery, anaesthesia and interaction with other drugs) may have had a significant influence on the determination of the carbon dioxide responsiveness. McQuay and colleagues (1979) demonstrated that, in 40% of their patients, the plasma fentanyl curves demonstrated secondary concentration peaks. Neither of these studies correlated the fentanyl plasma concentrations with respiratory variables of carbon dioxide response curves. McClain

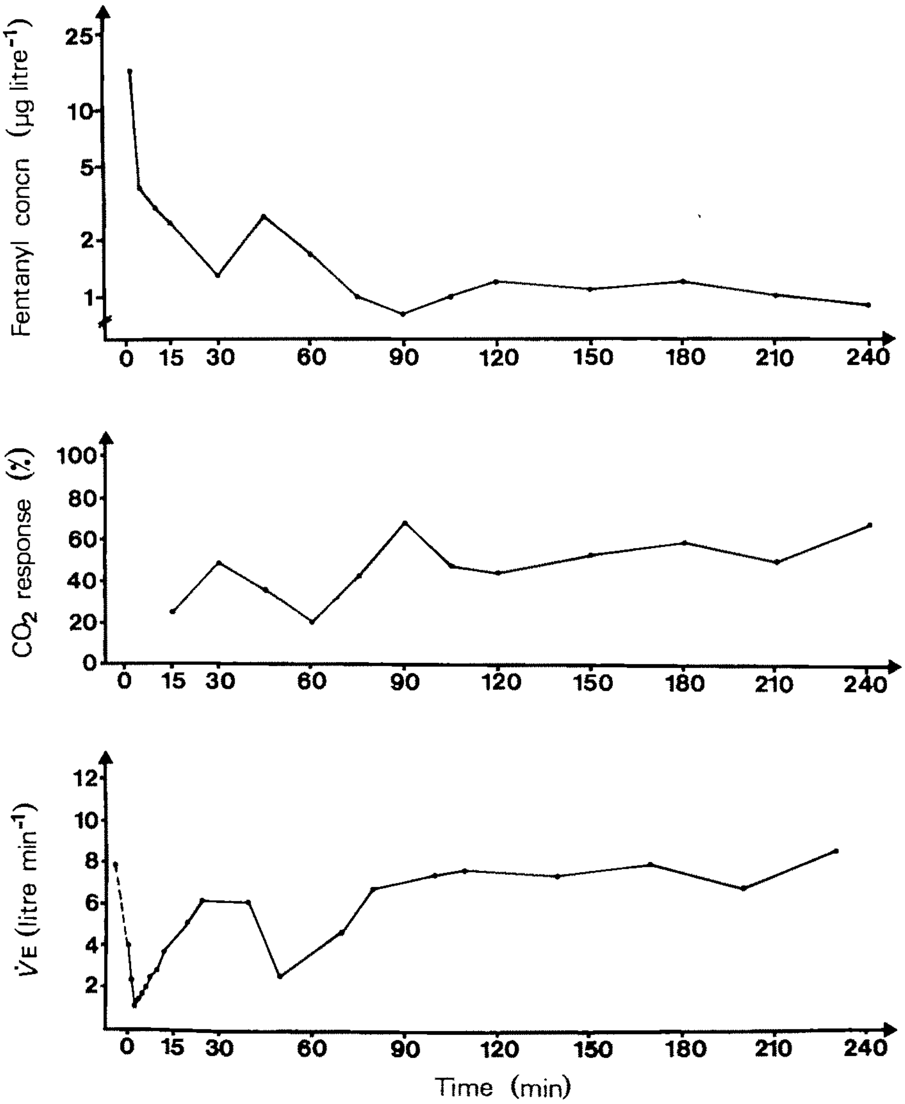

FIG. 3. Fentanyl plasma concentrations (upper panel); carbon dioxide response slopes as percentages of the control slope (middle panel); and minute ventilation (lower panel) in a volunteer (no. 3) with secondary respiratory depression after a single bolus injection of fentanyl 0.5 mg.

and Hug (1980) observed a close correlation between the mean values of plasma decay curves of fentanyl in volunteers and the mean of one ventilatory index taken from Harper and co-workers (1976).

In the present study a correlation has been achieved between the individual plasma fentanyl concentrations, particularly at the time of the second peak with several respiratory variables. Four of seven healthy volunteers showed secondary increases in plasma fentanyl concentrations which correlated with alterations in their carbon dioxide response curves. In addition, it was demonstrated in two of these four volunteers that the secondary increases in plasma concentration were responsible for clinically relevant respiratory insufficiency.

The question of time of onset and extent of the fentanyl rebound phenomenon is of clinical impor-

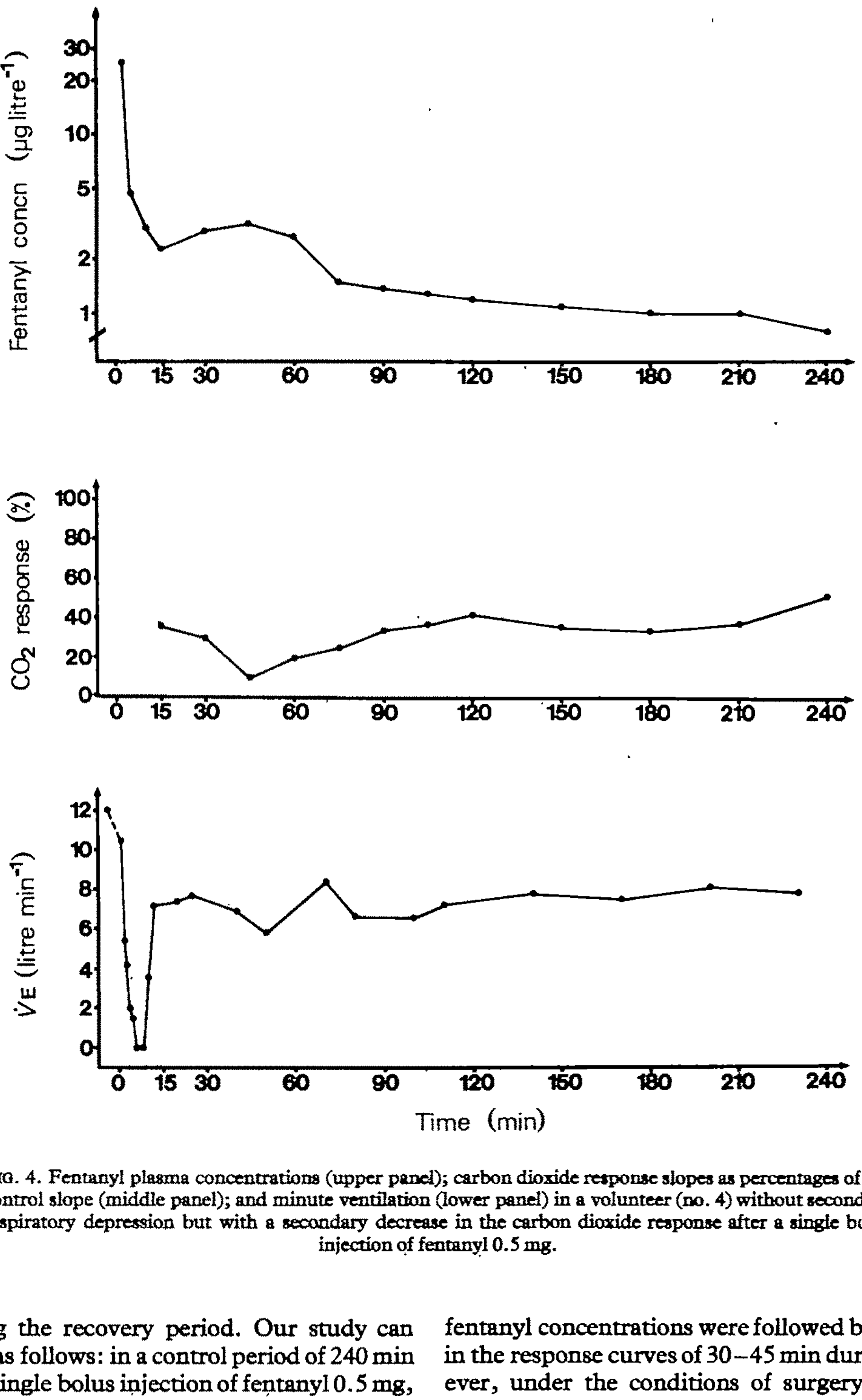

Fig. 4. Fentanyl plasma concentrations (upper panel); carbon dioxide response slopes as percentages of the control slope (middle panel); and minute ventilation (lower panel) in a volunteer (no. 4) without secondary respiratory depression but with a secondary decrease in the carbon dioxide response after a single bolus injection of fentanyl 0.5 mg.

tance during the recovery period. Our study can answer this as follows: in a control period of 240 min following a single bolus injection of fentanyl 0.5 mg, the secondary plasma peaks occurred between 45 and 90 min. These secondary increases in plasma fentanyl concentrations were followed by alterations in the response curves of 30–45 min duration. However, under the conditions of surgery and anaesthesia, these time intervals could be prolonged by alterations in the pharmacokinetics of fentanyl as a

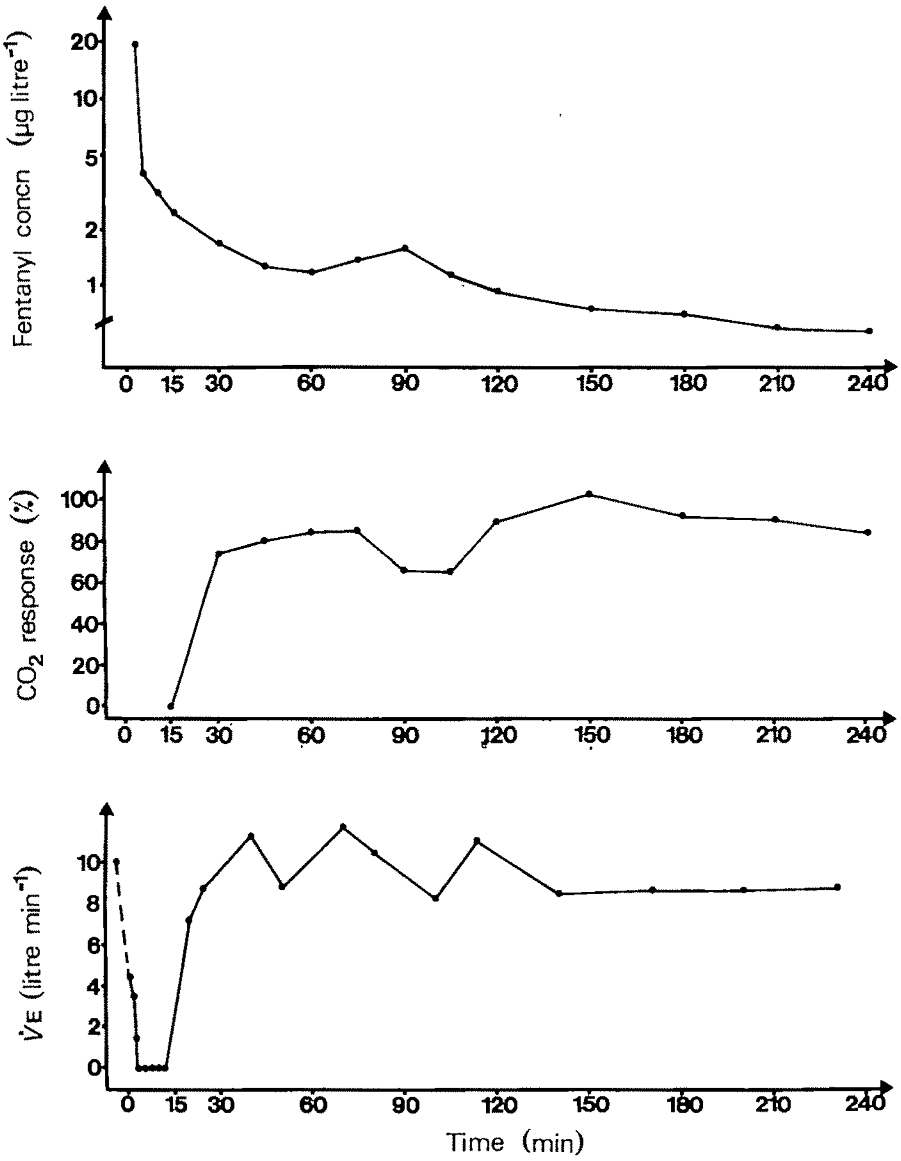

FIG. 5. Fentanyl plasma concentrations (upper panel); carbon dioxide response slopes as percentages of the control slope (middle panel); and minute ventilation (lower panel) in a volunteer (no. 5) without secondary respiratory depression but with a secondary decrease in carbon dioxide response after a single bolus injection of fentanyl 0.5 mg.

result of interactions with other drugs and alterations in the circulation. On the other hand, it is not possible to distinguish by the clinical observation of biphasic respiratory depression after anaesthesia supplemented by fentanyl, whether the recurrence of ventilatory insufficiency has to be explained by a pharmacokinetically-related recirculation phenomenon as studied by our group previously (Stoeckel, Hengstmann and Schüttler, 1979) and confirmed in this investigation, or by a prolonged depressant action of the drug having been interrupted by intermittent noxious stimuli in the recovery period as decribed by Becker and colleagues (1976).

ACKNOWLEDGEMENTS

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## REFERENCES

Adams, A. P., and Pybus, D. A. (1978). Delayed respiratory depression after use of fentanyl during anaesthesia. *Br. Med. J.*, **1**, 278.

Becker, L. D., Paulson, B. A., Miller, R. D., Severinghaus, J. W., and Eger, E. I. (1976). Biphasic respiratory depression after fentanyl–droperidol or fentanyl alone used to supplement nitrous oxide anesthesia. *Anesthesiology*, **44**, 291.

Cascorbi, H. F., and Gravenstein, J. S. (1974). Editorial views: Silent death. *Anesthesiology*, **40**, 319.

Downes, J. J., Kemp, R. A., and Lambertsen, C. J. (1967). The magnitude and duration of respiratory depression due to fentanyl and meperidine in man. *J. Pharmacol. Exp. Ther.*, **158**, 416.

Fung, D. L., and Eisele, J. H. (1980). Fentanyl pharmacokinetics in awake volunteers. *J. Clin. Pharmacol.*, **27**, 652.

Harper, M. H., Hickey, R. F., Cromwell, T. H., and Linwood, S. (1976). the magnitude and duration of respiratory depression produced by fentanyl and fentanyl plus droperidol in man. *J. Pharmacol. Exp. Ther.*, **199**, 464.

Kaufmann, R. D., Aqleh, K. A., and Bellville, J. W. (1979). Relative potencies and duration of action with respect to respiratory depression of intravenous meperidine fentanyl and alphaprodine in man. *J. Pharmacol. Exp. Ther.*, **208**, 73.

McClain, D. A., and Hug, C. C. (1980). Intravenous fentanyl kinetics. *Clin. Pharmacol. Ther.*, **28**, 106.

McQuay, H. J., Moore, R. A., Paterson, G. M. C., and Adams, A. P. (1979). Plasma fentanyl concentrations and clinical observations during and after operation. *Br. J. Anaesth.*, **51**, 543.

Michiels, M., Hendriks, R., and Heykants, J. (1977). A sensitive radioimmunoassay for fentanyl plasma level in dogs and man. *Eur. J. Clin. Pharmacol.*, **12**, 153.

Read, D. J. C. (1967). A clinical method for assessing the ventilatory response to carbon dioxide. *Austr. Ann. Med.*, **16**, 206.

Rigg, J. R. A., and Goldsmith, C. H. (1976). Recovery of ventilatory response to carbon dioxide after thiopentone, morphine and fentanyl in man. *Can. Anaesth. Soc. J.*, **23**, 370.

Stoeckel, H., Hengstmann, J. H., and Schüttler, J. (1979). Pharmacokinetics of fentanyl as a possible explanation for recurrence of respiratory depression. *Br. J. Anaesth.*, **51**, 741.

## CONCENTRATIONS PLASMATIQUES DE FENTANYL ET SURVENUE D'UNE DEPRESSION VENTILATOIRE CHEZ DES VOLONTAIRES.

### RESUME

Des volontaires bien portants ont reçu une dose unique de fentanyl i.v. 0,5 mg et la survenue d'une dépression respiratoire a été correllée aux pics secondaires de concentration plasmatique de fentanyl. Les concentrations plasmatiques de fentanyl, le volume courant, la ventilation minute, la $P\text{CO}_2$ de fin d'expiration, les pressions partielles des gaz du sang artériel et les courbes de réponse au $\text{CO}_2$ ont été déterminés pendant la période totale d'étude de 240 min. Des remontées secondaires des concentrations plasmatiques de fentanyl sont survenues chez quartorze des sept volontaires. Ces individus ont objectivé une dépression marquée de leurs courbes de réponse au $\text{CO}_2$ et chez deux d'entre eux l'insuffisance respiratoire était cliniquement évidente.

## PLASMA-FENTANYLKONZENTRATIONEN UND ATEMDEPRESSION BEI FREIWILLIGEN PROBANDEN

### ZUSAMMENFASSUNG

Gesunde Probanden erhielten Einzeldosen von Fentanyl 0,5 mg und es wurde das Auftreten von Atemdepression korrelliert mit sekundären Blutpeaks von Fentanyl. Die Plasmakonzentrationen von Fentanyl, das Atemzugvolumen, das endexpiratorische $P\text{CO}_2$, die arteriellen Blutgaswerte und die Antwortkurven auf $\text{CO}_2$ wurden während der Versuchsperiode von insgesamt 240 min bestimmt. Sekundäre Anstiege der Plasmakonzentrationen von Fentanyl traten bei vier der sieben Probanden auf. Diese vier Personen wiesen eine ausgeprägte Depression ihrer $\text{CO}_2$ Antwort-Kurven auf und bei zwei trat eine klinisch relevante Atemdepression auf.

## CONCENTRACIONES DE FENTANILO EN EL PLASMA Y OCURRENCIA DE DEPRESIONES VENTILATORIAS EN VOLUNTARIOS

### SUMARIO

Se administró dósis únicas de 0,5 mg de fentanilo i.v. a voluntarios sanos y se puso en correlación la ocurrencia de depresiones respiratorias con picos secundarios en las concentraciones de fentanilo en el plasma. Se determinaron durante el periodo total de estudio de 240 min., las concentraciones de fentanilo en el plasma, el volumen respiratorio, el volumenminuto, el $P\text{CO}_2$ respiratorio terminal, las tensiones arteriales sangre-gas y las curvas de respuesta al anhídrido carbónico. Ocurrieron aumentos secundarios en las concentraciones de fentanilo en el plasma en cuatro de los siete voluntarios. Estos cuatro individuos demostraron una depresión marcada de sus curvas de respuesta al anhídrido carbónico y en dos de ellos, era evidente desde el punto de vista clínico una insuficiencia respiratoria.

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# CHRONIC EXPOSURE OF RATS TO ENFLURANE 200 P.P.M.: NO EVIDENCE OF TOXICITY OR TERATOGENICITY

C. J. GREEN, S. J. MONK, J. F. KNIGHT, C. DORÉ,
N. P. LUFF AND M. J. HALSEY

## SUMMARY

Adult male or female rats were exposed either to enflurane 200 p.p.m. or to air for up to 63 days before mating and subsequently throughout the pregnancy of the females. The treated animals were exposed for 8 h per day, 5 days per week for a maximum total of 100 days. The parents and progeny were studied. Additional positive controls with vitamin A palmitate demonstrated that the strain of animals was susceptible to a known teratogen. No abortifacient effect was observed with these conditions of exposure to enflurane. Skeletal examination of the fetuses failed to reveal any major teratogenic effect. The parents remained healthy clinically, whilst autopsy and histopathological examination failed to reveal any consistent organ injuries which could be blamed on exposure to enflurane. In rats at least, environmental pollution with enflurane appears not to be associated with significant toxicity or teratogenicity.

In a recent study designed to test the possibility that chronic inhalation of enflurane 20 p.p.m. or of halothane 10 p.p.m. in air might affect fertility and cause fetotoxicity or teratogenicity (Halsey et al., 1981), we showed that such concentrations polluting the environment of adult male and female rats before mating for up to 64 days and then throughout pregnancy, produced no significant general toxicity, or abortifacient, teratogenic or fetotoxic effects under those experimental conditions. However, since enflurane has only recently been released for clinical use in this country, we felt that it should be tested more stringently at a higher pollution concentration and so carried out a similar study at 200 p.p.m.

To distinguish between any separate effects of enflurane on either spermatogenesis or oogenesis and fetal development, both male and nulliparous female rats were exposed to enflurane and then mated with unexposed rats. An equivalent comparison with halothane was not included in this series since halothane has already been tested at similar high concentrations both by ourselves (Lansdown et al., 1976) and others (Stevens et al., 1975). Enflurane-exposed animals were compared with controls subjected to identical environmental conditions lacking only the enflurane. As an additional check on the validity of this procedure, a test group of females was orally dosed with vitamin A palmitate during pregnancy to demonstrate that the strain of rats was susceptible to a known teratogen.

## MATERIALS AND METHODS

### *Animals and exposure chambers*

A total of 220 specified-pathogen-free Sprague–Dawley rats bred under barrier-maintained conditions in the Division of Comparative Medicine were marked, weighed and assigned to six experimental groups. Food and water were given *ad libitum* and consumption was measured weekly.

The animals were maintained in a controlled environment in the same two wooden-framed, double ply-wood skin chambers used previously (Halsey et al., 1981) with air recirculated at a flow rate of 5.5 litre $min^{-1}$ through a carbon dioxide absorber and temperature regulator. Oxygen and carbon dioxide were analysed automatically with alternate sampling of gases in the two chambers every 20 min. Each chamber was illuminated from 08.00 h to 16.00 h by three fluorescent lamps. Ambient wet and dry temperatures were measured with calibrated thermocouples every 20 min and in 1 week selected at random the mean temperature (standard error) was 19.2 (0.14) °C in the enflurane chamber and 19.6 (0.35) °C in the control chamber. Relative humidity was 75 (SEM 1.0%), carbon dioxide concentration was less than 0.5% and oxygen concentration ranged from 20.5 to 21.0%.

All aspects of the two sealed chambers were kept

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alike, but in one chamber, hereafter called the "enflurane chamber", enflurane was added to maintain a concentration of 200 p.p.m. for 8 h per day from 9 a.m. to 5 p.m., five consecutive days per week, via a separate circulation incorporating an enflurane vaporizer (Cyprane Ltd, Keighley, England). Enflurane concentration was monitored with a gas chromatograph (Perkin-Elmer F11 using a column of 8% carbowax W on Chromasorb W at 80 °C with a flame ionization detector) modified for automatic sampling of the gas every 20 min. Enflurane concentration in the chamber increased until 10.30 h when it was maintained until 17.00 h; on a sample day the measured concentration between these hours was 199 (SEM 5.6) p.p.m. Entrance to the chambers for husbandry, care and maintenance of the rats was restricted to periods when the animals were not exposed to enflurane, to avoid fluctuation in its concentration on opening the chamber door. This work was done at the same time each morning.

### *Experimental design*

*Group 1.* Twenty male rats (366 ± (SEM) 7 g) were kept in the enflurane chamber and exposed to enflurane 200 p.p.m. After 63 days, they were mated outside the chamber with 30 female rats (300 ± 5 g) immediately after the latter had been issued from the barrier-maintained breeding colony. After mating the male rats were returned to the enflurane chamber for a further 37 days, when they were killed and postmortems carried out. The females were kept in the control chamber until day 21 of pregnancy.

*Group 2.* Twenty male rats (367 ± 7 g) were kept in the control chamber. After 63 days, they were mated outside the chamber with 30 female rats (308 ± 6 g) freshly issued from the breeding colony. The males were then returned to the control chamber for a further 37 days before being killed for postmortem. Females were kept in the control chamber until day 21 of pregnancy.

*Group 3.* Twenty female rats (239 ± 4 g) were kept in the enflurane chamber for 28 days before being mated outside the chamber with 20 males from the breeding colony. The females were then returned to the enflurane chamber until day 21 of pregnancy.

*Group 4.* Twenty female rats (245 ± 3 g) were kept in the control chamber for 28 days and then mated with 20 males from the breeding colony. They were then returned to the control chamber until day 21 of pregnancy.

*Group 5.* Twenty pregnant female rats (303 ± 19 g) transferred from the breeding colony on day 1 of pregnancy to the control chamber received by mouth vitamin A palmitate in arachis oil (Roche Products Ltd, Welwyn Garden City) 30 000 iu day$^{-1}$ (0.1 ml day$^{-1}$) on days 5 – 13 of gestation, inclusive.

*Group 6.* Twenty pregnant female rats (311 ± 23 g) transferred from the breeding colony on day 1 of pregnancy to the control chamber received orally arachis oil 0.1 ml day$^{-1}$ (Roche Products Ltd) on days 5 – 13 of gestation, inclusive.

### *Sampling and measurements*

*Postmortem examination of female adults.* Female rats were killed, weighed and examined 1 day before scheduled natural parturition and weights of maternal liver and kidneys were recorded. Samples of maternal liver, kidney and lung were fixed and stained with haemotoxylin and eosin for light microscopy. The gravid uteri were opened and examined, and placental weights, fetal weights, crown – rump length, sex, number and gross abnormalities were recorded. Fetal loss was measured by the number of resorptions, dead fetuses and deciduomata without implants. Females which were not pregnant were also sacrificed and the uteri inspected for resorptions. All fetuses were fixed in 95% ethanol for alazarin red S staining and skeletal preparation before examination for assessment of osseous development and skeletal abnormalities (Fritz and Hess, 1970).

Skeletal abnormalities were classified under the broad headings in table III.

*Postmortem examination of male adults.* Male rats from groups 1 and 2 were killed and weighed after 100 days in the enflurane or control chamber. Samples of paternal liver, kidney, lung, spleen, testes and heart were fixed in 10% formal saline, sectioned and then stained with haematoxylin and eosin for histological examination.

*Statistical analysis.* The data were subjected to statistical analysis by the same methods described in our previous communication (Halsey et al., 1981). Analysis of variance was used to estimate the components of variance between and within litters and hence provide an estimate of the variance of the mean of a litter of given size (Healey, 1972). Student's *t* test was then used to compare control and anaesthetic groups and to compare the positive control groups 5 and 6, using the reciprocal of the variance to weight the mean of each litter. Values from each comparison of control and anaesthetic groups were combined to give an overall test of significance (Winer, 1971). When only one observation was made on each experimental unit then either Student's *t* test or a comparison of proportions was used to compare the control and anaesthetic groups.

## RESULTS

### *Enflurane and air groups*

The effects of each treatment on pregnancy and litter loss are summarized in table I. In each group a number of females were found not to be pregnant at postmortem examination and a total of six females gave birth before the planned Caesarean section. This reduced the number of dams with 21-day-old fetuses available for comparison. It was noted that only four of the non-pregnant females were expected to be pregnant—having been mated with proven males and a definite vaginal plug having been formed—and these were with males that had been exposed to air (group 2).

Details of the litters and fetal measurements are summarized in tables I and II. Overall, no significant differences can be detected when comparing groups of rats exposed to enflurane with their respective controls. The total number of fetuses with skeletal abnormalities in each group (table III) ranged from 15 to 40. This apparently high frequency mainly reflects the number of fetuses with supplementary vestigial ribs and reduced phalangeal ossification.

A total of three gross abnormalities revealed by skeletal staining occurred in treated (group 1) and control animals (group 2). One fetus was found in each with two feet on the left hind limb (that is, 10 toes) and one fetus in group 1 exhibited faulty ossification with only the posterior portion of the cranium ossified and the cervical and thoracic vertebrae extended laterally. The frequencies are too small to have any statistical significance. There was no obvious association between those litters with

TABLE I. *Chronic exposure to enflurane: mean (SEM) litter size and fetal losses*

| | Group | | | | |
|---|---|---|---|---|---|
| | 1 Males in enflurane | 2 Males in air | 3 Females in enflurane | 4 Females in air | Sig. of combined analysis |
| No. of female rats originally | 30 | 30 | 20 | 20 | — |
| No. pregnant | 25 | 22 | 16 | 18 | — |
| No. of litters examined | 23 | 21 | 15 | 16 | — |
| Total no. of live fetuses | 305 | 285 | 191 | 226 | n.s. |
| Implantations/dam | 13.7<br>(0.8) | 13.7<br>(0.8) | 14.0<br>(0.7) | 14.9<br>(0.5) | n.s. |
| Live/litter | 13.3<br>(0.9) | 13.6<br>(0.8) | 13.6<br>(0.7) | 14.1<br>(0.5) | n.s. |
| % Resorptions | 3.2 | 1.0 | 0.0 | 0.8 | n.s. |
| % Deciduomata | 0.0 | 0.0 | 2.6 | 2.9 | n.s. |
| % Dead *in utero* | 0.0 | 0.0 | 0.0 | 1.3 | n.s. |

TABLE. II. *Chronic exposure to enflurane: fetal and placental data (mean (SEM))*

| | Group 1 | Group 2 | Group 3 | Group 4 | Significance of combined analysis |
|---|---|---|---|---|---|
| Fetal weight (g) | 5.54 (0.12) | 5.30 (0.13) | 5.78 (0.14) | 5.78 (0.13) | n.s. |
| Placental weight (g) | 0.60 (0.03) | 0.61 (0.03) | 0.57 (0.03) | 0.56 (0.03) | n.s. |
| Fetal/placental weight ratio | 9.7 (0.4) | 9.3 (0.4) | 10.3 (0.5) | 10.9 (0.5) | n.s. |
| Crown – rump length (cm) | 4.07 (0.05) | 3.98 (0.06) | 4.22 (0.05) | 4.22 (0.05) | n.s. |
| % Males | 48 (4) | 47 (3) | 53 (3) | 46 (4) | n.s. |

TABLE III. *Chronic exposure to enflurane: classification and number of skeletal abnormalities. Total loss during skeletal preparation: 0.8%.* **P < 0.01; ***P < 0.001

| | | Group | | | |
|---|---|---|---|---|---|
| | | 1 Males in enflurane | 2 Males in air | 3 Females in enflurane | 4 Females in air |
| Phalanges: | Reduced ossification or missing | 11** | 24 | 12 | 12 |
| Ribs: | Supplementary | 1*** | 17 | 11*** | 4 |
| | Wavy | 0 | 0 | 2 | 0 |
| Sternebrae: | True sternebrae partially or unossified | 0 | 0 | 2 | 0 |
| | Manubrium partially or unossified | 0 | 0 | 2 | 0 |
| | Xiphisternum partially or unossified | 0 | 0 | 3 | 0 |
| | Bipartite ossification | 0 | 2 | 0 | 0 |
| | Extra sternebrae | 1 | 0 | 1 | 3 |
| Vertebrae: | Partially ossified or missing | 0 | 0 | 0 | 1 |
| | Extra vertebrae | 0 | 1 | 1 | 0 |
| Gross skeletal abnormalities | | 2 | 1 | 0 | 0 |
| Total no. of abnormalities | | 15*** | 45 | 34** | 20 |
| Total no. of abnormal fetuses | | 15*** | 40 | 29** | 20 |
| Total no. of 21-day gestation fetuses inspected | | 305 | 279 | 188 | 222 |
| Fetuses with abnormalities (%) | | 14.92 | 14.34 | 15.43 | 9.01 |
| No. of litters with two or more abnormal fetuses | | 3 | 7 | 8 | 5 |
| No. of litters with both abnormal and resorbed fetuses | | 1 | 0 | 1 | 1 |

abnormal fetuses and those with resorptions. For example, there was a 1% frequency of resorptions in group 2 (table I), but none of the resorptions occurred in litters which also had abnormal fetuses (table III).

Chronic exposure to enflurane 200 p.p.m. had no significant effect on the increase in body weight (expressed as a percentage) of either male or female rats. Nor could any effect on maternal or paternal liver weight be demonstrated. Exposed females had slightly enlarged left kidneys ($P < 0.05$), but it is difficult to see how unilateral enlargement can be of biological significance, especially as no effect could be demonstrated in the kidneys of exposed males.

Water and food intake were measured from the day each group of rats was placed in a controlled environment to the day they were paired. It was expressed as intake per gram of initial body weight. Male rats exposed to enflurane consumed 5.6 ml $g^{-1}$ of water and 3.4 g $g^{-1}$ of food, whilst those in the control chamber used 5.2 ml $g^{-1}$ of water and 3.3 g $g^{-1}$ of food. Similarly no significant effect of exposure could be demonstrated in females, those exposed to enflurane using 3.6 ml $g^{-1}$ of water and 3.3 g $g^{-1}$ of food whereas control rats used 3.1 ml $g^{-1}$ and 3.3 g $g^{-1}$ respectively.

The histology of maternal and paternal organs is summarized for groups 1 – 4 in table IV. Small foci of hepatic necrosis, fatty degeneration and mononuclear cell infiltrates could be found in livers from all groups and were not related to enflurane exposure, pregnancy or sex of the rats. Indeed, there were somewhat fewer normal livers in control rats than in treated animals. Kidneys from male rats were normal but, in contrast, kindeys from females had a high frequency of either acute or chronic tubular necrosis which was not related to anaesthetic exposure or to pregnancy. Lesions were severe in a high proportion of these kidneys. Chronic respiratory disease occurred equally in male and female

TABLE IV. *Chronic exposure to enflurane: histology of male and female rats*

| | Group | | | | | |
|---|---|---|---|---|---|---|
| | Male | | Female (non-pregnant) | | | |
| | 1 | 2 | 1 | 2 | 3 | 4 |
| Livers: | | | | | | |
| Mononuclear cell infiltrate | 7 | 8 | 8 (+2) | 13 (+6) | 6 (+1) | 7 (+2) |
| Fatty degeneration | 1 | 10 | 0 | 1 | 0 | 0 |
| Centrilobular degeneration and vacuolation | 1 | 0 | 2 (+1) | 0 | 0 | 0 |
| Normal | 8 | 4 | 13 (+1) | 7 (+1) | 9 (+3) | 10 |
| No. examined | 16 | 20 | 23 (+4) | 21 (+7) | 15 (+4) | 17 (+2) |
| Kidneys: | | | | | | |
| Chronic necrosis | 0 | 0 | 18 (+4) | 16 (+6) | 4 (+3) | 8 (+1) |
| Acute tubular necrosis | 0 | 0 | 7 | 4 (+1) | 1 | 1 (+1) |
| Mononuclear cell infiltrate | 0 | 0 | 0 | 0 | 0 | 0 |
| Glomerular nephritis | 0 | 1 | 0 | 0 | 1 | 0 |
| Normal | 16 | 19 | 2 | 2 | 9 (+1) | 7 |
| No. examined | 16 | 20 | 24 (+4) | 21 (+7) | 15 (+4) | 17 (+2) |
| Lungs: | | | | | | |
| Chronic respiratory disease | 13 | 17 | 7 (+2) | 9 (+2) | 12 (+2) | 16 (+2) |
| Acute inflammation | 0 | 0 | 4 | 2 | 0 | 0 |
| Normal | 3 | 3 | 14 (+2) | 10 (+5) | 4 (+1) | 1 |
| No. examined | 16 | 20 | 24 (+4) | 21 (+7) | 15 (+4) | 17 (+2) |

animals, but again showed no correlation with enflurane exposure. Testes and spleens of males all appeared normal.

*Positive controls*

Treatment with vitamin A palmitate produced an increased frequency of macroscopic fetal abnormalities—anencephaly and cleft palate (table V). In the treated group 87% of the fetuses had skeletal abnormalities which were mainly classified as supplementary ribs, partially ossified or missing vertebrae, unossified manubrium and xiphisternum (table VI).

Postmortem and histological examination of the maternal livers demonstrated small foci of mononuclear cells in both groups. Some of the kidneys had acute tubular necrosis which was often accompanied by calcification. However, there were no apparent treatment-related histological differences in the dams.

## DISCUSSION

As in our earlier studies with halothane (Lansdown et al., 1976) and enflurane at a smaller, more realistic pollution concentration of 20 p.p.m. (Halsey et al., 1981), the pregnancy rate in the present studies ranged between 70 and 90%, but this bore no relation to anaesthetic exposure of either female or male rats. Nor could significant differences be traced in any of the comparisons of total live fetuses obtained,

TABLE V. *Vitamin A on days 5–13 of pregnancy: litter and fetal data (mean (SEM)).* $^*P < 0.03$; $^{**}P < 0.001$

| | Group 5 | Group 6 |
|---|---|---|
| Oral dose | Vitamin A palmitate in arachis oil (300 000 iu ml$^{-1}$) | Arachis oil |
| Daily dose | 0.1 ml | 0.1 ml |
| No. females | 20 | 20 |
| No. litters examined | 16 | 18 |
| No. live fetuses | 226 | 208 |
| Implantations/dam | 14.1 (0.7) | 11.6 (0.87)* |
| Live/litter | 12.3 (0.65) | 11.2 (0.9) |
| % Resorptions | 13.3 | 8.7 |
| Fetal weight (g) | 3.36 (0.20) | 3.65 (0.20) |
| Placental weight (g) | 0.62 (0.02) | 0.64 (0.02) |
| Fetal/placental weight ratio | 5.5 (0.3) | 5.9 (0.3) |
| Crown–rump length (cm) | 3.48 (0.08) | 3.55 (0.08) |
| % Male | 47.9 (4.2) | 50.6 (4.1) |
| % Anencephalic | 24 | 0** |
| % Cleft palate | 3.6 | 0* |

TABLE VI. *Vitamin A on days 5–13 of pregnancy: classification and number of skeletal abnormalities.* $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$

| | | Group 5 | Group 6 |
|---|---|---|---|
| Phalanges: | Reduced ossification or missing | 14 | 7 |
| Ribs: | Supplementary or wavy | 153 | 24*** |
| | Fused | 3 | 0 |
| Sternebrae: | True sternebrae partially or unossified | 3 | 1 |
| | Manubrium partially or unossified | 33 | 12** |
| | Xiphisternum partially or unossified | 33 | 17* |
| Vertebrae: | partially ossified or missing | 15 | 1** |
| Anencephalic | | 41 | 0*** |
| Total no. of abnormalities | | 295 | 62 |
| Total no. of abnormal fetuses | | 170 | 40*** |
| Total no. of 21-day fetuses inspected | | 196 | 186 |
| Fetuses with abnormalities (%) | | 87 | 22 |

number of live fetuses per litter or numbers of implantations per dam. Indeed, these are surprisingly constant throughout the groups with less variation than was observed in our earlier studies. The frequency of resorption varied from 0 to 3.2%. However, there were no significant differences between the groups and the maximum frequency observed in this study is relatively low for this strain of rat.

The susceptibility of these rats to a known teratogen, vitamin A, was checked, with results similar to those of others (Morriss and Steele, 1977; Morriss, 1979), so the animal model is considered sound. Overall these conclusions are consistent with earlier studies on possible effects of enflurane on reproduction (Strout et al., 1977; Wharton and Mazze, 1979).

Chronic exposure to enflurane had no obvious deleterious effect on the health of the animals whether judged on clinical symptoms, gross post-mortem findings or histological examination. Mild chronic respiratory disease developed in all groups in spite of their isolation within a controlled environment and care in transfer initially from the barrier-maintained breeding colony to fumigated chambers. No treatment-related lesions could be detected in lung sections.

There were differences in the frequencies of minor skeletal abnormalities. However, in the males, the enflurane treated group actually had a lower frequency than their respective controls. The reduced phalangeal ossification probably reflected the inclusion of a small number of fetuses harvested before full-term. In the females the enflurane treated group had an increased frequency which was associated primarily with supplementary ribs. Although a difference of this magnitude in the females is statistically significant, it is of doubtful teratological importance. It is known that in this strain there is spontaneous occurrence of this type of abnormality (Lansdown et al., 1976). There are also differences between the control groups which may reflect seasonal and other changes in the breeding conditions. However, the positive control data demonstrate that the effect of a known teratogen is much more dramatic (table VI). The possibility of a low frequency of production of minor abnormalities associated with enflurane cannot be conclusively disproved. However, the present results do not justify the very large sample sizes that would be necessary to take into account the background genetic variability.

It also proved impossible to identify any specific hepatic toxicity with exposure. There were no significant changes in liver weight in any of the rats, male or female. Under light microscopy, there were more observable lesions in livers from control males than any other group, and certainly no evidence to incriminate enflurane as hepatotoxic at this concentration. These data are in keeping with previous findings in rats (Harrison et al., 1976; Stevens et al., 1977) and recent findings in dogs and monkeys exposed to enflurane at 1.5 MAC for up to 36 h or prolonged repeated administration of subanaesthetic concentrations (0.01 MAC) for 4 weeks (Clark et al., 1979). In the latter study, halothane apparently produced histopathological changes in liver associated with deterioration in hepatic function tests, whereas enflurane did not.

Just as in our previous series where we found moderate to severe renal lesions in female but not male rats from control as well as halothane and enflurane-exposed groups, the female rats in the present study also exhibited severe lesions of either acute or chronic tubular necrosis whether from control or treated groups. Whilst this is an interesting observation, it has apparently no correlation either with exposure to enflurane or with pregnancy. Although it has been claimed in the past that enflurane may be nephrotoxic in some circumstances (Dvoracek et al., 1974; Cousins et al., 1976), it is likely that kidney lesions were produced in those animal experiments by a combination of prolonged exposure to near anaesthetic concentrations of enflurane and severe hypoxia (Dvoracek et al., 1975). Biotransformation of enflurane yields only low quantities of inorganic fluoride (Chase et al., 1971; Cousins and Mazze, 1974; Greenstein, Hitt and Mazze, 1975) so it is unlikely to have such severe effects on tubular epithelium as, for example, methoxyflurane. Indeed, more recent experiments in animals have failed to demonstrate renal toxicity in dogs or monkeys (Clark et al., 1979) and investigations in man have shown that renal dysfunction is not a problem after enflurane anaesthesia in well-ventilated patients with normal kidney function (Cousins et al., 1976; Corall, Knights and Strunin, 1977; Weiss and de Carlini, 1977). Our data provide further evidence that enflurane is not nephrotoxic even after prolonged exposure to relatively high pollution concentrations. On the basis of the combined clinical, postmortem and histopathological evidence, the present study suggests that the threshold for chronic toxicity already established for continuous exposure to enflurane for 4 weeks (Stevens et al., 1977) is not decreased if the animals are exposed daily for periods up to nearly 4 months.

We believe that chronic exposure to enflurane 200 p.p.m. represents a severe test. For instance, the concentration of 200 p.p.m. probably represents a pollution level 30 times the mean anaesthetic contamination of the worst location in a recent survey of U.K. hospitals (Davenport et al., 1980). Whereas other workers (Wharton et al., 1978, 1979) have applied the concept of MAC-hours to chronic toxicity testing, there is direct evidence that chronic exposure to lower concentrations can represent a more severe toxicity stress than acute exposure to high concentrations (discussed in Halsey, 1981). This could admittedly have been rendered even more stressful if the animals had been exposed continuously, but the experiments would not then have mimicked occupational exposure of theatre staff, and inconsistent loss of appetite would probably have introduced nutritional artefacts to the results. In this species at least, enflurane passes the test, lacking fetotoxicity, teratogenicity and toxicity to sensitive tissues such as the liver, kidney and testes.

## CONCLUSIONS

The present experiments failed to demonstrate any enflurane-related fetal or histological toxicity after exposure to enflurane 200 p.p.m. for 8 h per day, 5 days per week over a period of nearly 4 months. These data taken in conjunction with those available from other studies in experimental animals and in man suggest that, in terms of chronic toxicity and environmental pollution, enflurane is as safe or safer than other halogenated volatile anaesthetics currently available. Although, admittedly, our case is proven in one species of animal only there seems little justification for doing further tests on enflurane in rodents.

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## REFERENCES

Chase, R. E., Holaday, D. A., Fiserova-Bergerova, V., Saidman, L. J., and Mack, F. E. (1971). The biotransformation of ethrane in man. *Anesthesiology*, 36, 262.

Clark, G. C., Kesterson, J. W., Coombs, D. W., Cherry, C. P., Prentice, P. E., and Kohn, F. E. (1979). Comparative effects of repeated and prolonged inhalation exposure of beagle dogs and cynomolgus monkeys to anaesthetic and subanaesthetic concentrations of enflurane and halothane. *Acta Anaesthesiol. Scand.*, 71, 1.

Corall, I. M., Knights, K. M., and Strunin, L. (1977). Enflurane (Ethrane) anaesthesia in man: metabolism and effects on biochemical and haematological variables. *Br. J. Anaesth.*, 49, 881.

Cousins, M. J., and Mazze, R. I. (1974). Biotransformation of enflurane (Ethrane) and isoflurane (Forane). *Int. Anesthesiol. Clin.*, 12, 11.

—— Greenstein, L. R., Hitt, B. A., and Mazze, R. I. (1976). Metabolism and renal effects of enflurane in man. *Anesthesiology*, 44, 44.

Davenport, H. T., Halsey, M. J., Wardley-Smith, B., and Bateman, P. E. (1980). Occupational exposure to anaesthetics in 20 hospitals. *Anaesthesia*, 35, 354.

Dvoracek, B., De Bruijn, W. C., Blok, A. P. R., Faithfull, N. S., and Ducardus, R. (1975). Renal tubular changes following anaesthesia in pigs: a comparison of nitrous oxide and enflurane; in *Recent Progress in Anaesthesiology and Resuscitation* (ed. A. Arias), p. 193. Amsterdam: Excerpta Medica.

—— Ducardus, R., Van Haelst, U. J. M., Kubat, K., and Van der Pluijm, W. J. M. (1974). The effects of Ethrane on renal function and experimental comparison with penthrane in pigs; in *Ethrane* (eds P. Lawin and R. Beer), p. 158. Berlin: Springer-Verlag.

Fritz, H., and Hess, R. (1970). Ossification of the rat and mouse skeleton in the perinatal period. *Teratology*, 3, 331.

Greenstein, L. R., Hitt, B. A., and Mazze, R. I. (1975). Metabolism *in vitro* of enflurane, isoflurane and methoxyflurane. *Anesthesiology*, 42, 420.

Halsey, M. J. (1981). Studying toxicity of inhaled general anaesthetics. *Br. J. Anaesth.*, 53, 57S.

Halsey, M. J., Green, C. J., Monk, S. J., Doré, C., Knight, J. F., and Luff, N. P. (1981). Maternal and paternal chronic exposure to enflurane and halothane: fetal and histological changes in the rat. *Br. J. Anaesth.*, 53, 203.

Harrison, G. G., Marsh, J. A., Bradshaw, J. J., Zietsman, I., and Ivenetich, K. M. (1976). Some aspects of the hepatic metabolism of Ethrane. *S. A. Med. J.*, 50, 2080.

Healey, M. J. R. (1972). Animal litters as experimental units. *Appl. Stats.*, 21, 155.

Lansdown, A. G. B., Pope, W. D. B., Halsey, M. J., and Bateman, P. E. (1976). Analysis of fetal development in rats following maternal exposure to subanaesthetic concentrations of halothane. *Teratology*, 13, 299.

Morriss, G. M. (1979). Teratogenesis; in *Maternal Effects in Development* (eds D. R. Newth and M. Balls), p. 351. Cambridge: University Press.

—— Steele, C. E. (1977). Comparison of the effects of retinol and retinoic acid on postimplantation rat embryos *in vitro*. *Teratology*, 15, 109.

Stevens, W. C., Eger, E. I., White, A., Biava, C. G., Gibbons, R. D., and Shargel, R. (1977). Comparative toxicities of enflurane, fluroxene and nitrous oxide at subanaesthetic concentrations in laboratory animals. *Can. Anaesth. Soc. J.*, 24, 479.

—— —— —— Halsey, M. J., Munger, W. L., Gibbons, R. D., Dolan, W. M., and Shargel, R. (1975). Comparative toxicities of halothane, isoflurane and diethyl ether at subanesthetic concentrations in laboratory animals. *Anesthesiology*, 42, 408.

Strout, C. D., Nahrwold, M. L., Taylor, M. D., and Zagon, I. S. (1977). Effects of subanesthetic concentrations of enflurane on rat pregnancy and early development. *ASA Annual Meeting Scientific Abstracts*, p. 555.

Weiss, J., and de Carlini, C. (1977). Enflurane metabolism and postoperative renal function. *Anaesthesist*, 26, 130.

Wharton, R. S., and Mazze, R. I. (1979). Reproductive safety of enflurane in female mice. *Anesthesiology*, 51, 261.

—— —— Baden, J. M., Hitt, B. A., and Dooley, J. R. (1978). Fertility, reproduction and postnatal survival in mice chronically exposed to halothane. *Anesthesiology*, 48, 167.

—— Wilson, A. I., Mazze, R. I., Baden, J. M., and Rice, S. A. (1979). Fetal morphology in mice exposed to halothane. *Anesthesiology*, 51, 532.

Winer, B. J. (1971). *Statistical Principles in Experimental Design*, 2nd edn, p. 49. Koga Kusha: McGraw-Hill.

## EXPOSITION CHRONIQUE DE RATS A L'ENFLURANE 200 p.p.m.: AUCUN SIGNE DE TOXICITE OU DE TERATOGENICITE

### RESUME

Des rats adultes males ou femelles ont été exposés soit à l'enflurane 200 p.p.m. soit à l'air pendant des périodes atteignant 63 jours avant l'accouplement et ensuite pendant toute la durée de la grossesse des femelles. Les animaux traités étaient exposés 8 par jour, 5 jours par semaine, pendant un nombre total maximum de 100 jours. Les parents et la progéniture ont été étudiés. Des contrôles supplémentaires positifs avec du palmitate de Vitamine A ont montré que la souche d'animaux était sensible à un produit connu comme tératogène. Aucun effet abortif n'a été observé dans ces conditions d'exposition à l'enflurane. L'examen du squelette des foetus n'a révélé aucun effet tétatogéne majeur. Les parents sont restés cliniquement sains, tandis que l'autopsie et l'examen anatomopathologique n'ont montré aucune ésion organique notable qui aurait pu être attribuée à une exposition à l'enflurane. Chez le rat tout au moins, la pollution de l'environnement par l'enflurane ne semble pas entraîner de toxicité ou de tératogénécité significatives.

## EXPOSICIÓN CRÓNICA DE RATAS A 200 PPM DE ENFLURANO: NO HAY PRUEBA DE TOXICIDAD NI TAMPOCO DE TERATOGENICIDAD

### SUMARIO

Estuvieron expuestas ratas, machos o hembras, ya sea a 200 ppm de enflurano o al aire por un periodo de hasta 63 días antes de aparearse y luego durante todo el embarazo de las hembras. Los animales tratados se encontraban expuestos por 8 h. al día, 5 días por semana durante un periodo total máximo de 100 días. Se llevó a cabo un estudio de los padres y de su prole. Controles positivos adicionales con palmitato de vitamina A demostraron que la ascendencia de los animales era susceptible a un teratógeno conocido. No se observó ningún efecto abortivo en esas condiciones de exposición al enflurano. El examen del esqueleto de los fetos no reveló ningún efecto teratogénico mayor. Los padres permanecieron sanos desde el punto de vista clínico, mientras que la autopsia y el examen histopatológico no revelaron lesiones orgánicas constantes de cualquier índole que hubieran podido atribuirse a la exposición al enflurano. En ratas por lo menos, la contaminación del medio ambiente por enflurano no parece tener vínculos con una toxicidad o teratogenicidad significativas.

## CHRONISCHE EXPOSITION VON RATTEN MIT 200 P.P.$^{m}$ ENFLURAN: KEINE EVIDENZ VON TOXIZITÄT ODER TERATOGENIZITÄT

### ZUSAMMENFASSUNG

Erwachsene weibliche oder mänliche Ratten wurden entweder 200 p.p.$^{m}$. Enflurane oder Luft ausgesetzt bis zu 63 Tage vor der Paarung und weiter während der Schwangerschaft der Weibchen. Die behandelten Tiere wurden 8 Stunden pro Tag und 5 Tage pro Woche und insgesamt höchstens 100 Tage exponiert. Die Eltern und die Nachkommenschaft wurden untersucht. Zusätzliche positive Kontrollen mit Vitamin A-Palmitat zeigten, daß der Tierstamm gegenüber einem bekannten Teratogen empfindlich war. Keine abortiven Wirkungen wurden unter diesen Bedingungen der Enflurane Exposition beobachtet. Skelett-Untersuchungen der Feten decten keine größere teratogene Wirkung auf. Die Eltern blieben klinisch gesund und Autopsie und histopathologische Untersuchung deckten keinen bleibenden Organschaden auf, die auf die Enflurane-exposition zuruckzuführen gewesen wäre. Zumindest bei Ratten scheint die Umweltverschmutzung mit Enflurane nicht mit signifikanter Toxizität oder Teratogenizität einherzugehen.

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# EFFERENT VAGAL DISCHARGE AND HEART RATE IN RESPONSE TO METHOHEXITONE, ALTHESIN, KETAMINE AND ETOMIDATE IN CATS

K. INOUE AND J. O. ARNDT

## SUMMARY

The effects of methohexitone, Althesin, ketamine and etomidate on single fibre discharge of cardiac vagal efferents and on heart rate were studied in cats. Cardiac vagal efferents were inhibited markedly and regularly for equihypnotic doses of methohexitone (2.0 mg kg$^{-1}$), Althesin (0.1 ml kg$^{-1}$) and ketamine (5.0 mg kg$^{-1}$), but not of etomidate (0.8 mg kg$^{-1}$). These inhibitory effects were independent of arterial pressure and mirrored the increases of heart rate elicited by the first three agents. Etomidate did not consistently affect cardiac vagal discharge or heart rate. Thus methohexitone, Althesin and ketamine inhibit efferent cardiac vagal drive by their central action independently of baroreflex function. This central vagolysis is probably the cause of their positive chronotropic effects.

I.v. anaesthetics such as barbiturates, steroids and phencyclidine derivatives cause tachycardia in man and animals (Arndt and Zindler, 1978).

Since all these agents slow the isolated heart (Reynolds, Chiz and Pasquet, 1970; Fischer, 1973; Fischer and Marquort, 1977) and most of them also markedly inhibit efferent sympathetic nerve activity (Millar et al., 1970; Skovsted, Price and Price, 1970; MacKenzie et al., 1976; Skovsted and Sapthavichaikul, 1977) the tachycardia seems to result from an inhibition of cardiac vagal drive. However, the mechanism is not generally agreed. The arterial hypotension usually associated with anaesthesia has tacitly been considered the prime mover which, via baroreflex, would inhibit vagal cardiac tone, but there is no direct proof for this notion and the hypertensive action of ketamine, for example, is certainly not compatible with such a view.

This study was undertaken to analyse the effects of i.v. anaesthetics on cardiac vagal drive and it will be shown that they attenuate markedly the activity of cardioinhibitory neurones independently of baroreflex function.

## METHODS

The analysis of the effects of i.v. anaesthetics on efferent vagal activity was performed on 58 cats with a body weight between 2.0 and 4.2 kg. In these experiments, vagal transmission to the heart was blocked by vagal dissection in the course of fibre dissection and the use of the muscle relaxant, pancuronium. We therefore evaluated the heart rate response to these agents in additional experiments on awake cats with intact vagal cardiac innervation and, for comparison, also during nitrous oxide anaesthesia.

*Anaesthesia.* For induction of anaesthesia, the animals were placed in an airtight box into which 3–4% halothane in nitrous oxide in oxygen (3:1) was administered. After intubation of the trachea, the lungs were ventilated with a Starling pump to provide an end-expiratory carbon dioxide concentration of about 4% measured continuously by mass-spectrometry (Perkin Elmer MGA 1100). Surgery, which required 2 h on average to prepare for nerve activity recording was performed under 0.5–1.5% halothane in nitrous oxide in oxygen (3:1). Halothane was discontinued at least 1 h before starting nerve activity recording and the animals were immobilized with pancuronium, 0.2 mg kg$^{-1}$ i.v. initially and 0.1 mg kg$^{-1}$ i.v. supplements as needed, so that the actual experiments were performed under nitrous oxide in oxygen (3:1). The animals with an intact vagal innervation, in which the heart rate responses to the agents were analysed using nitrous oxide anaesthesia, received suxamethonium 1 mg kg$^{-1}$ i.v. intermittently instead of pancuronium.

Body temperature was maintained at 37.5±0.5 °C with a heating lamp.

*Recording of nerve activity.* The right cervical

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vagus was dissected free in the neck, covered with paraffin oil at body temperature to prevent drying and filamented under a microscope until single active fibres were obtained from central nerve bundles separated from the nerve trunk. Spikes were picked up with bipolar platinum–iridium electrodes and amplified with a capacitance-coupled amplifier of our own design which had an input impedance of 22 MΩ and a bandpass between 30 and 35 000 Hz.

Nerve activity was monitored with a loudspeaker and an oscilloscope (Tektronix type 565). The spikes were shaped to standard pulses (5 V, 0.5 ms duration) with a Schmitt trigger to trigger reliably a digital counter of our own design which produced a spike count at 2.5- or 5-s intervals. To calculate the average discharge rate (spikes $s^{-1}$), the 2.5- or 5-s values were averaged for periods of 10–30 s. The technical details of the spike processing system have been described in detail (Arndt, Morgenstern and Samodelov, 1977).

*Parameters measured.* Arterial pressure was measured electromanometrically (Statham P 37 B) with a fluid-filled catheter advanced into the thoracic aorta from a femoral artery and heart rate with a cardiotachometer triggered by the e.c.g.

All data were recorded continuously on a multichannel pen-recorder (Beckmann type RM dynograph recorder).

*Identification of cardiac and non-cardiac vagal efferents.* Various vagal efferents (named type A, B and C in the present study) were identified according to their response to a brief increase in arterial pressure induced by occlusion of the descending aorta with an inflatable balloon (Fogarty biliary probe No. 5; fig. 1): *type A* activity increased when arterial pressure was increased. Such fibres, the discharge of which has been shown to correlate inversely with heart rate (Jewett, 1964; Inoue, Samodelov and Arndt, 1980), are considered to be cardioinhibitory. *Type B* activity decreased with increasing arterial pressure. *Type C* activity remained unchanged in spite of increasing arterial pressure.

Types B and C are non-cardiac, although their target organs were not identified.

*Evaluation of the drug effects.* The drug effects on type A fibres were evaluated in two different ways: (1) From the time-course of average discharge rate following drug injections either independently of arterial pressure or at arterial pressures kept at or greater than the pre-injection values by inflation of the aortic balloon. (2) By comparing pressure–response curves determined before and 2 min after drug injections. These pressure–response curves were derived by relating average discharge rates with various arterial pressures increased or decreased relative to the control pressure by inflat-

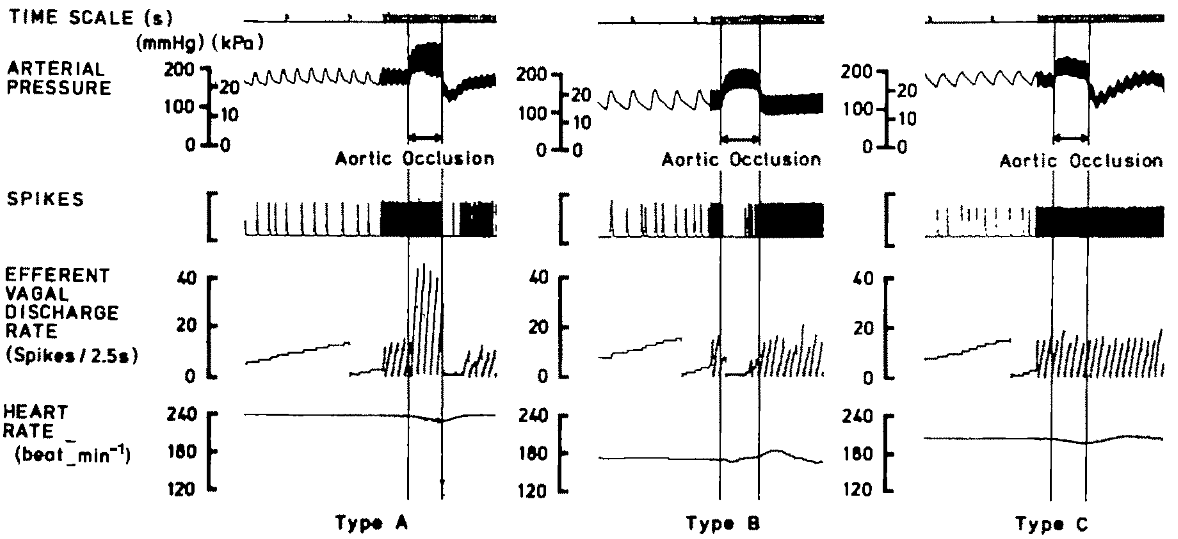

FIG. 1. Responses of various vagal efferents to an induced hypertension. Original recordings from three cats under nitrous oxide in oxygen anaesthesia. The transient increase in arterial pressure by aortic occlusion leads to an increase (type A), decrease (type B) or no change in fibre discharge (type C).

ing or by rapidly deflating the aortic balloon (fig. 1).

Responses of non-cardiac type B and type C efferents to the drugs were evaluated qualitatively and judged as activation, no change or inhibition.

The following doses were used: methohexitone 2.0 mg kg$^{-1}$, Althesin 0.1 ml kg$^{-1}$, ketamine 5.0 mg kg$^{-1}$ and etomidate 0.8 mg kg$^{-1}$. They were found to be equipotent according to pilot experiments in awake cats.

*Experimental procedure.* The experiments were started at least 1 h after surgery when nerve activity, arterial pressure and heart rate were in a steady state and when several pressure–response curves were identical. Each drug was administered within 3 s through a catheter placed in the right atrium. The drugs were administered in random sequence and sufficient time, usually 45 min, was allowed between each injection for complete recovery of the variables studied.

In the experiments for the evaluation of the chronotropic effects of the agents in anaesthetized cats, each drug was given in the same way as above, but at least 5 min after the injection of suxamethonium to avoid interference with cardiovascular effects of the muscle relaxant.

*Data analysis.* To demonstrate the time-course of the drug effects on discharge rate of cardioinhibitory vagal efferents the data are expressed as percentages of the values before injection for each individual fibre.

The pressure–response curves were constructed for each individual fibre before and after drug injection. The discharge rates and corresponding arterial pressures were averaged to derive the average pressure–response curves.

The data are presented in means ± SEM except for the time-course of the drug effects. The differences between values before and after injection were

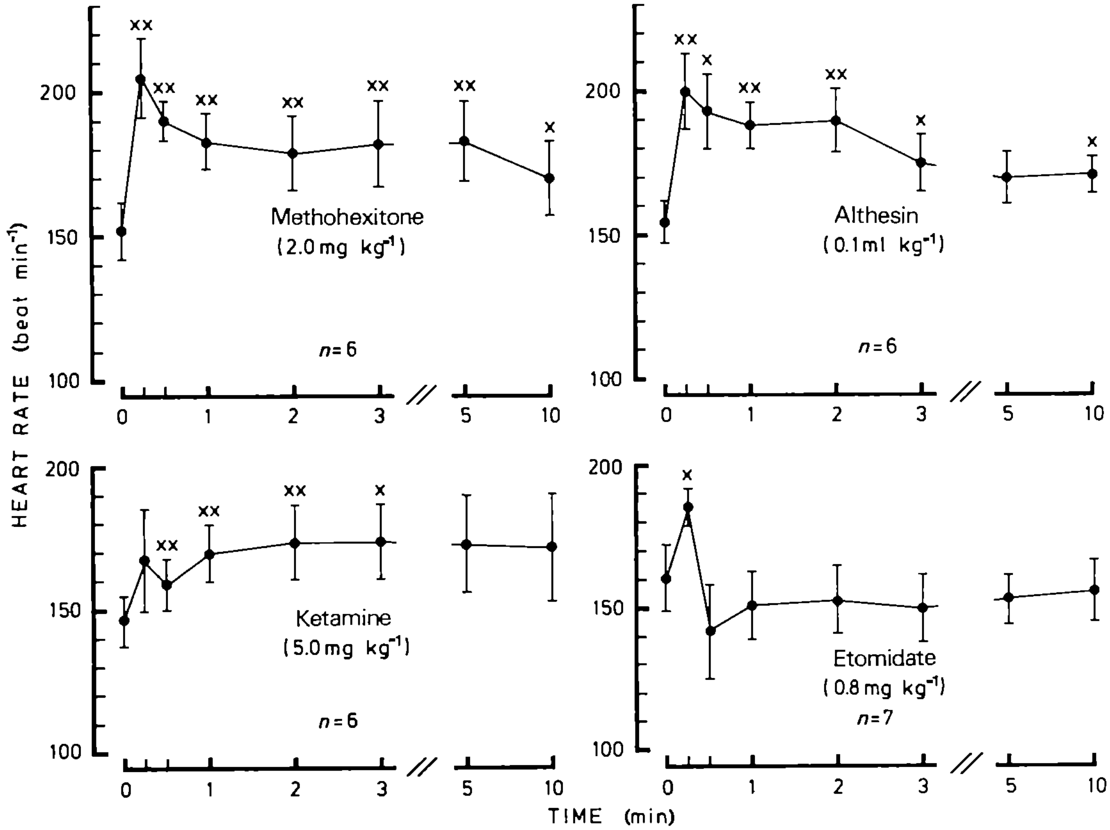

FIG. 2. Heart rates after i.v. injections of the four anaesthetics in awake cats (mean ± SEM). Significance test between the controls and postinjection values: × $P<0.05$; × × $P<0.01$.

tested with Student's *t* test for paired samples, since each cat served as its own control. Differences were considered significant when $P < 0.05$.

## RESULTS

*Hypnotic and chronotropic effects of the drugs in awake cats.* The doses used were found to be equipotent in their hypnotic effects by pilot studies on awake cats. Awake cats lay down, closed their eyes, and lost their righting reflexes within 5–25 s after injection and woke up 4–6 min later as judged by their ability to raise their heads and open their eyes.

As is seen in figure 2, this was accompanied by an abrupt increase in heart rate by about 40 beat $min^{-1}$ within 30 s after injection of methohexitone and Althesin. With ketamine, the increase in heart rate by about 20 beat $min^{-1}$ developed gradually and reached its maximum 2 min after injection. Etomidate had no consistent effect except for a transient increase immediately after the injection.

*Drug effects on cardiac vagal efferents in anaesthetized cats.* The discharge rates of cardioinhibitory vagal efferents always decreased with methohexitone, Althesin and ketamine, but their responses to etomidate were unpredictable. As shown in original recordings (fig. 3), the average discharge rates are much less after than before the injection of methohexitone, Althesin and ketamine, but there was hardly a response to etomidate.

To exclude the initial, transient decrease in arterial pressure seen in figure 3 as a possible factor for a baroreflex-mediated vagal inhibition, the decrease in pressure was prevented by balloon occlusion of the descending aorta in some experiments.

In the example shown in figure 4, vagal discharge rate clearly decreased following methohexitone in spite of constant arterial pressure and with Althesin and ketamine even when arterial pressure was increased. The last is worth stressing because increased arterial pressure by itself in the absence of anaesthetics activates vagal discharge of type A

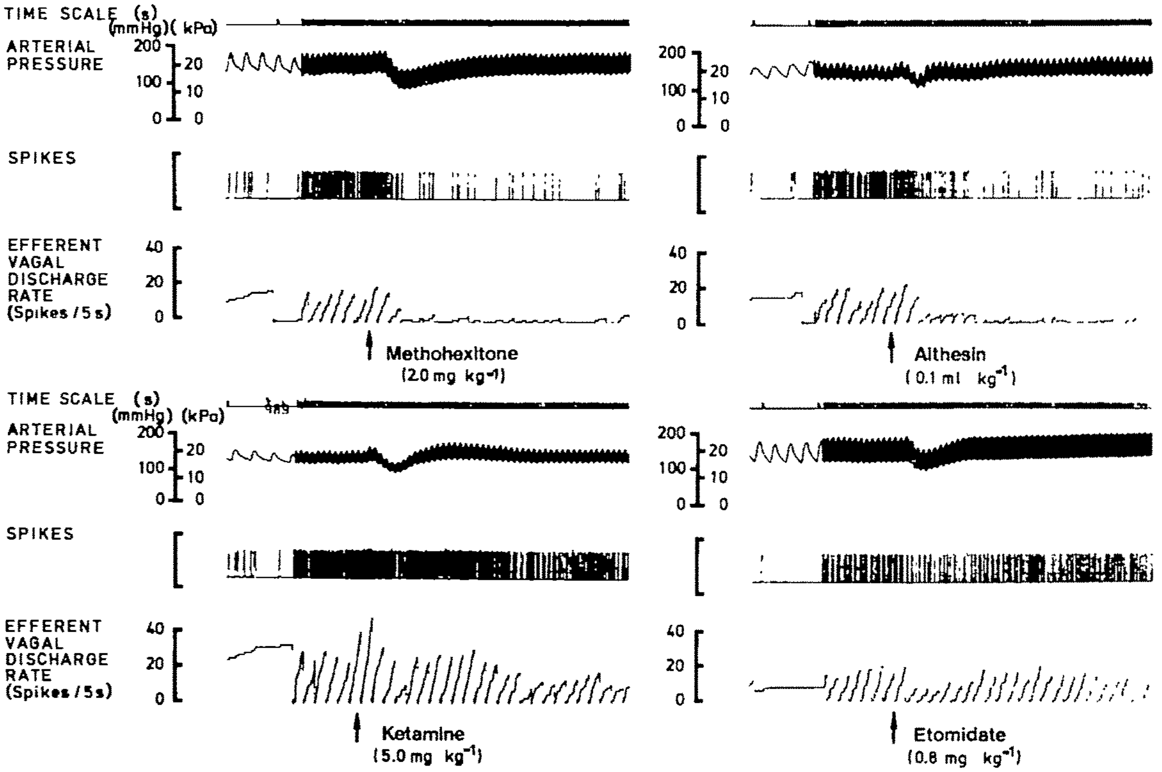

FIG. 3. Effects of the four anaesthetics on discharge rates of cardioinhibitory vagal efferents. Original recordings from four cats under nitrous oxide in oxygen anaesthesia.

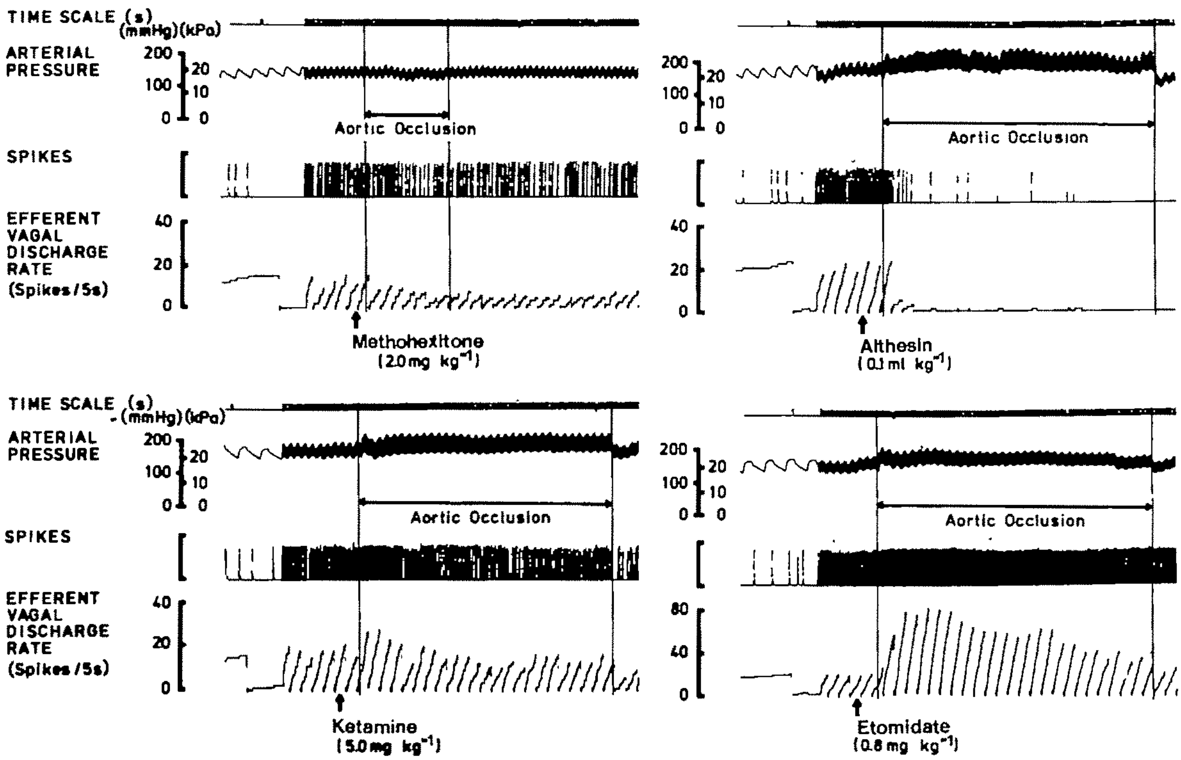

FIG. 4. Effects of the four anaesthetics on discharge rates of cardioinhibitory vagal efferents with constant or slightly increased arterial pressure. Original recordings from three cats under nitrous oxide in oxygen anaesthesia. The initial decrease in arterial pressure seen in figure 3 was prevented here by controlled balloon occlusion of the descending aorta.

fibres (fig. 1). Such an activation, in fact, is seen with etomidate in figure 4.

Methohexitone, Althesin and ketamine had similar effects in all experiments, as is seen in figure 5. Irrespective of whether the early decrease in arterial pressure was prevented, discharge rate decreased without exception during the first 5 min after injections of these three agents and returned gradually to the controls during the following 30 min. In contrast to this, etomidate did not produce regular changes in discharge rates, irrespective of the arterial pressure. The differences in the time courses of vagal activity are also of interest. After injections of methohexitone and Althesin, discharge rates attained their minimum rapidly during the 1st min, but more slowly within 2 min following ketamine. We considered it therefore appropriate to compare the inhibitory action of these agents for their values 2 min after injections, particularly since, at this time, arterial pressure had reached the pre-injection values in all experiments.

For quantitative analysis of the fibre response, pressure–response curves were determined for each cardioinhibitory fibre before and 2 min after drug injections. The original recording in figure 6 shows how these response curves were derived. In the control, nerve discharge rate increased above the preocclusion value when arterial pressure was increased for about 25 s by inflating the aortic balloon and decreased below the preocclusion value when the balloon was deflated. Clearly, 2 min after the injection of ketamine, average discharge rate was less for each arterial pressure value which was of the same magnitude as during the control. Thus, ketamine inhibits nerve activity independently of arterial pressure.

Figure 7 was obtained by relating discharge rates and the corresponding pressure values before and 2 min after injections for each fibre. Except for etomidate, the pressure–response curves are dis-

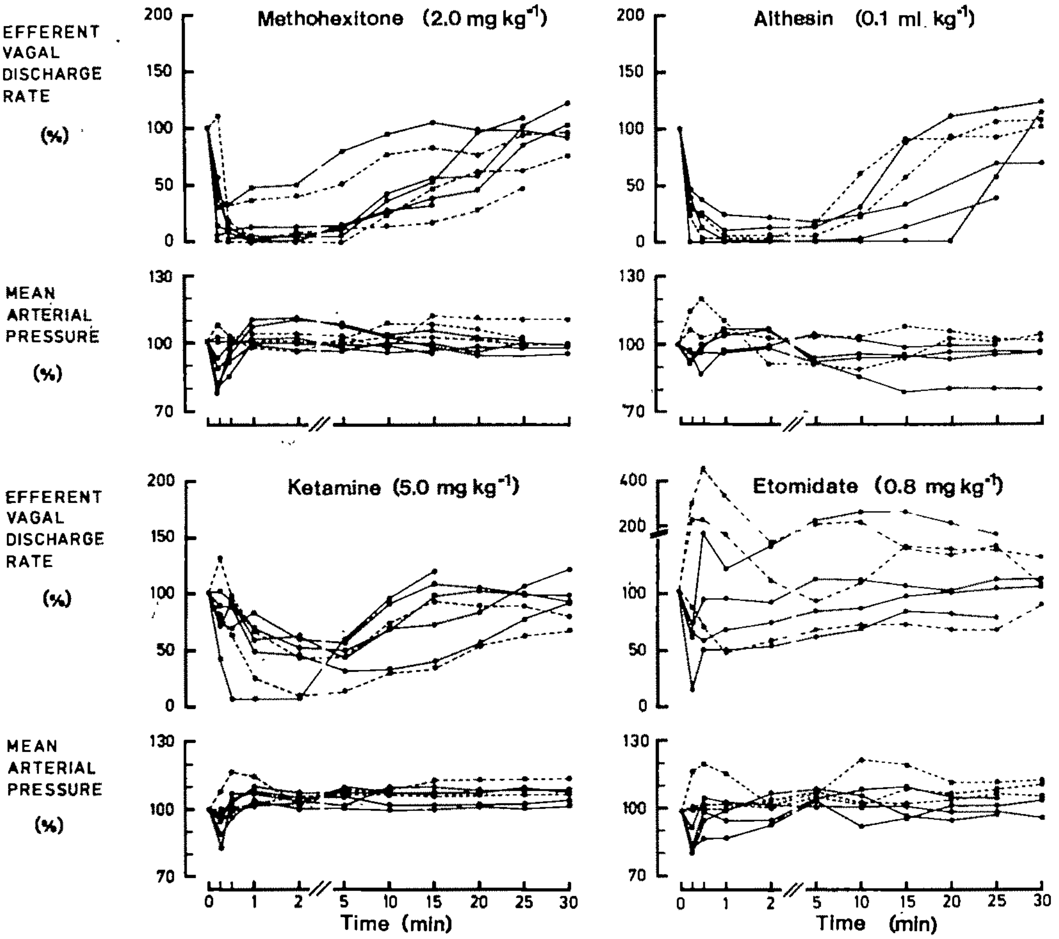

FIG. 5. Time course of the discharge of cardioinhibitory vagal efferents following the injection of the four anaesthetics. Data from 19 cats under nitrous oxide in oxygen anaesthesia. The initial decrease in arterial pressure was either not prevented (continuous lines) or was prevented by aortic occlusion (dotted lines).

placed to lower activity and their slopes are reduced. Methohexitone, Althesin and ketamine not only inhibit vagal discharge independently of arterial pressure but, in addition, they also inhibit the pressure-dependent fibre response as indicated by the reduced slopes.

Taking the average discharge rate at the control pressures (centre point of the curves) as 100, the activity is reduced by 90, 73 and 55% for Althesin, methohexitone and ketamine, respectively. Thus, for equipotent doses, the extent of the pressure-independent, central inhibition of vagal cardioinhibitory efferents is different for various agents. It is most marked with Althesin, followed by methohexitone and ketamine, whereas etomidate has no effect.

*Drug effects on non-cardiac vagal efferents in anaesthetized cats.* Non-cardiac fibres responded less uniformly to the anaesthetics than the cardiac. According to table I, inhibition prevailed with methohexitone and Althesin which, however, had no effect on about one-third of type C fibres. This non-uniformity was more pronounced with ketamine. It inhibited only a minority of non-cardiac fibres, had no effect in about half of them and even activated some. The response-pattern of non-cardiac fibres agreed with that of the cardiac only in case of etomidate. Thus, the same anaesthetic may act differently on different neurones (type A, B and C) whereas the particular cardioinhibitory type A

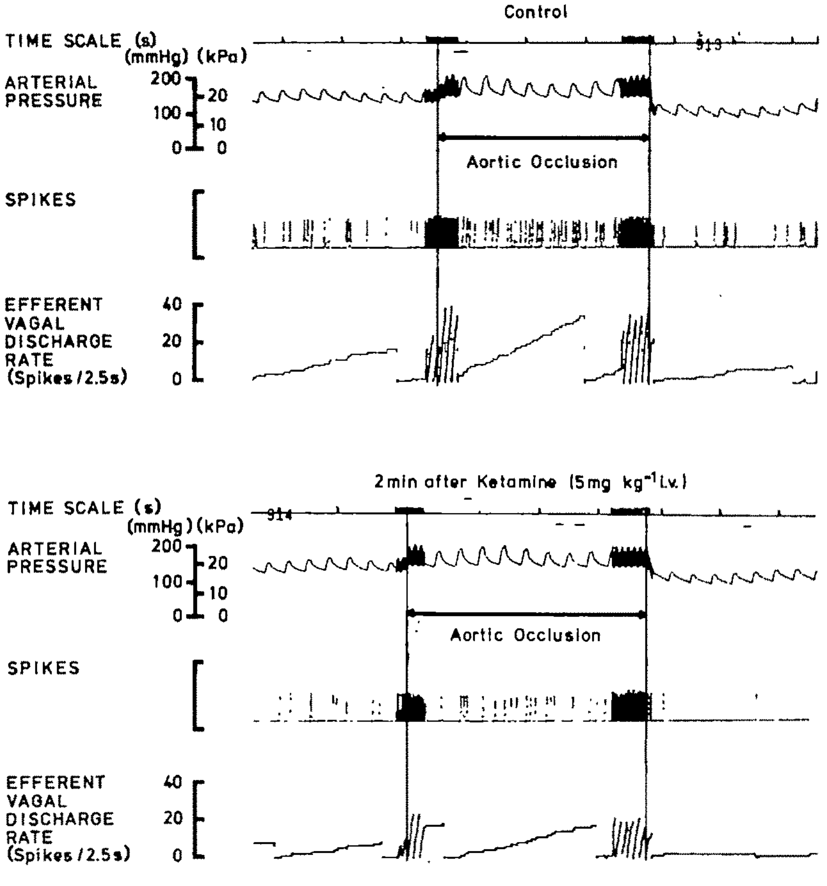

FIG. 6. The discharge of a cardioinhibitory vagal fibre at three different arterial pressures before and 2 min after injection of ketamine. Original recording from a cat under nitrous oxide in oxygen anaesthesia. Arterial pressures were altered by controlled occlusion of the descending aorta by a balloon.

neurone is inhibited by various anaesthetics (methohexitone, Althesin and ketamine).

*Chronotropic effects of the agents in anaesthetized cats with intact cardiac vagal innervation.* The chronotropic effects could not be analysed in these experiments because of the atropine-like action of pancuronium and the disruption of the vagal nerves in the course of fibre dissection. Therefore, it was necessary to evaluate the heart rate responses to the agents in cats with an intact vagal innervation, but otherwise under similar conditions.

According to table II, the heart rate increased 2 min after injections of methohexitone, Althesin and ketamine by 36, 52 and 23 beat min$^{-1}$, respectively, and there was on average no change with etomidate. These effects correspond, by and large, with our observation in awake cats shown in figure 2.

## DISCUSSION

Our experiments were primarily designed to study the effects of anaesthetics on cardiac vagal drive and a central question is if the fibres of which responses were tested here, do innervate the heart. In general, it is difficult to identify the organ specificity of vagal efferents. Such differentiation has been attempted according to their response to variations in arterial pressure and lung mechanics. In spontaneously breathing dogs, Jewett (1964) discriminated seven

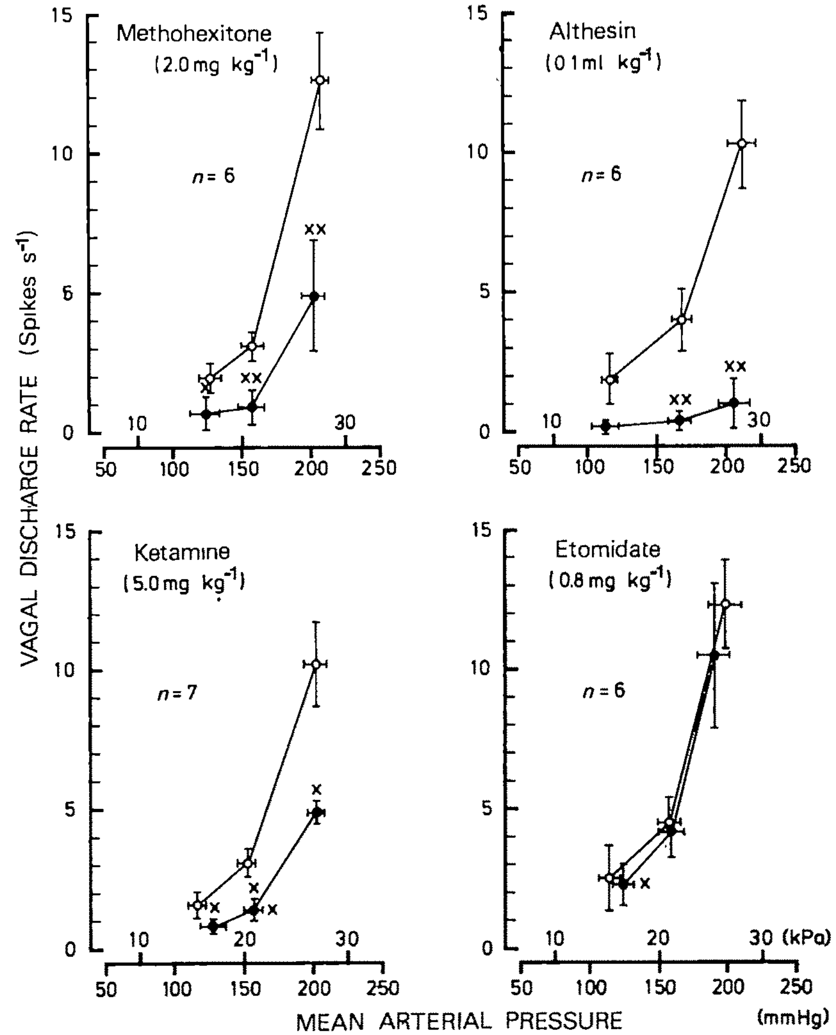

FIG. 7. Pressure–response curves of cardioinhibitory vagal efferents in the control (○) and 2 min after the injection (●) of the four anaesthetics. Results from cats under nitrous oxide in oxygen anaesthesia (mean ± SEM). Significance test between the controls and postinjection values. × $P<0.05$; × × $P<0.01$.

different fibre groups. His type I fibres were activated only during expiration, their discharge increased with increasing arterial pressure and correlated inversely with heart rate. In Jewett's view, which was later adopted by several others (Katrona et al., 1970; Hakumäki, 1972; Davidson, Goldner and McCloskey, 1976) these fibres are cardioinhibitory. Since we worked with ventilated and paralysed cats, neither lung mechanics nor the heart rate response which was blocked by the vagolytic action of the muscle relaxant, could be taken into consideration. Nevertheless, our type A fibres conform to Jewett's type I in one important point, in that they were not only activated by an increase in arterial pressure, but their discharge followed without delay the induced arterial pressure change and correlated closely with the arterial pressure as shown by the pressure–response curves in figure 7. By these criteria, the type A fibres the discharge rate of which has previously been shown to correlate with heart rate (Inoue, Samodelov and Arndt, 1980), could be distinguished clearly from non-cardiac vagal fibres.

TABLE I. *Effects of the four anaesthetics on activities of various vagal efferents*

| Fibre | Response | Methohexitone 2.0 mg $kg^{-1}$ | Althesin 0.1 ml $kg^{-1}$ | Ketamine 0.5 mg $kg^{-1}$ | Etomidate 0.8 mg $kg^{-1}$ |
|---|---|---|---|---|---|
| Type A | Inhibition | 8/8 | 6/6 | 7/7 | 3/7 |
| | Activation | — | — | — | 3/7 |
| | No change | — | — | — | 1/7 |
| Type B | Inhibition | 5/5 | 3/3 | 2/4 | 2/4 |
| | Activation | — | — | 1/4 | 2/4 |
| | No change | — | — | 1/4 | — |
| Type C | Inhibition | 11/16 | 12/17 | 3/13 | 4/11 |
| | Activation | — | — | 3/13 | 2/11 |
| | No change | 5/16 | 5/17 | 7/13 | 5/11 |

TABLE II. *Heart rate (beat* $min^{-1}$*) after injections of the four anaesthetics (mean ± SEM).* $^{*}P < 0.05$, $^{**}P < 0.01$

| Drug | Time after injection (min) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | 0.25 | 0.5 | 1 | 2 | 3 | 5 | 10 |
| Methohexitone 2.0 mg $kg^{-1}$ ($n = 6$) | 158±8 | 177±9<br>** | 195±3<br>** | 194±4<br>** | 194±5<br>** | 193±5<br>** | 191±5<br>** | 184±5<br>* |
| Althesin 0.1 ml $kg^{-1}$ ($n = 6$) | 155±14 | 180±12<br>** | 197±13<br>** | 204±13<br>** | 206±13<br>** | 207±13<br>** | 207±13<br>** | 192±17<br>** |
| Ketamine 5.0 mg $kg^{-1}$ ($n = 6$) | 159±10 | 188±12<br>** | 180±12<br>* | 183±11<br>* | 182±11<br>* | 181±11<br>* | 179±11<br>** | 176±12<br>n.s. |
| Etomidate 0.8 mg $kg^{-1}$ ($n = 6$) | 161±12 | 173±11<br>n.s. | 173±12<br>n.s. | 168±13<br>n.s. | 164±13<br>n.s. | 162±14<br>n.s. | 160±14<br>n.s. | 161±11<br>n.s. |

Our non-cardiac type B and C fibres which were either inhibited or not affected by the induced arterial pressure change, contained a variety of fibres. Since we were only interested to observe how these non-cardiac fibres would respond to anaesthetics in comparison with cardioinhibitory type A fibres, no further attempts were made to identify their target organs.

The atropine-like action of pancuronium and vagal dissection in the course of the nerve filamentation blocked the effects on heart rate which were seen after drug injection in conscious and anaesthetized cats with intact vagal innervation. Irrespective of the actual heart rate response, the type A fibres are cardioinhibitory and their activity may be taken as a neurophysiological correlate of cardiac vagal tone.

Nitrous oxide, which renders cats analgesic without impairing evoked potentials in the brain, has been advocated as the most suitable anaesthetic for neurophysiological work (Venes, Collins and Taub, 1971). It was preferred also because there is evidence that nitrous oxide does not alter the heart rate effects of other anaesthetics. In man, the heart rate increased little (2.65%) when nitrous oxide was added to light halothane anaesthesia (0.8–1.2% in oxygen) and by even less (0.82%) when nitrous oxide was added to deep halothane anaesthesia (1.2–2.0% in oxygen) (Smith et al., 1970). Finally, in dogs, addition of nitrous oxide to halothane anaesthesia (0.5–2.5% in oxygen), elicited the same degree of bradycardia found with halothane in oxygen (Smith and Corbascio, 1966). It appears reasonable to interpret the described responses of the type A fibres as the drug action *per se* rather than as a consequence of their additive action with nitrous oxide.

Methohexitone, Althesin and ketamine, but not etomidate, inhibited without exception cardioinhibitory vagal efferents. These fibres originate from the vagal nuclei in the medulla, the nucleus ambiguus and vagalis dorsalis (Spyer, 1980), and their discharge constitutes the neurophysiological correlate of cardiac vagal tone and thus of heart rate (Jewett, 1964). In the dose range used in this study, none of these agents exerts an atropine-like peripheral action (McGrath, MacKenzie and Millar, 1975; MacKenzie et al., 1976). All have a negative chronotropic effect on the isolated heart (Reynolds, Chiz and Pasquet, 1970; Fischer, 1973; Fischer and Marquort, 1977) and, with the exception of ketamine, all inhibit efferent sympathetic drive (Millar et al., 1970; Skovsted, Price and Price, 1970; MacKenzie et al., 1976; Skovsted and Sapthavichaikul, 1977). The positive chronotropic actions of these agents are therefore the consequence of an inhibition of cardiac vagal drive. This applies also to ketamine, which activates efferent sympathetic drive (Niederstrasser, 1981) but the action of which in producing tachycardia is nevertheless blocked by atropine rather than by propranolol (Traber, Wilson and Priano, 1970a, b).

In our neurophysiological studies, the drug effects on heart rate could not be identified. When cardiac vagal innervation was intact, the heart rate responded similarly in the conscious state and under nitrous oxide anaesthesia. Under both conditions, the tachycardia, in correspondence with the degree of vagal inhibition, was most pronounced with Althesin followed by methohexitone and ketamine whereas etomidate had no effect. It seems permissible, therefore, to consider the responses of cardiac vagal efferents to these agents as a principal cause of their heart rate effects.

The inhibition of vagal efferents was shown to be independent of arterial pressure as it occurred at constant and even at increased pressure, which usually activates these fibres. This conclusion is also supported by the clear-cut displacement of the pressure–response curves to lower activities with all agents except etomidate. Pressure-dependent effects via arterial baroreflexes cannot, therefore, explain the fibre responses.

Also probably excluded are drug-induced changes in baroreceptor activity which, in the presence of constant arterial pressure, might have altered afferent baroreceptor drive. Methohexitone, for example, excites baroreceptors (Schumacher and Arndt, 1978). This, however, should activate cardiac vagal efferents but not inhibit them. Ketamine has no effect on baroreceptors (Slogoff and Allen, 1974; Hagenau, Pietsch and Arndt, 1976), but nevertheless inhibits vagal efferents. A peripheral event via the afferent discharge of arterial baroreflexes is therefore an unlikely causal factor for the inhibitory action of these agents on cardiac vagal tone. Hence one can conclude that, contrary to the widely held view, the vagolytic action of certain i.v. anaesthetics is of central origin and independent of arterial pressure and baroreflex function.

This conclusion does not, however, deny the importance of baroreflexes in anaesthesia. In fact, the well-known impairment of baroreflex function (Morrison, Walker and Richardson, 1950; Bristow et al., 1969; MacKenzie et al., 1976) is seen also in our experiments in the reduced slopes of the pressure–response curves of cardioinhibitory vagal efferents, which are particularly pronounced with methohexitone and Althesin. This shows that these agents, in addition to their central vagolytic effects, also attenuate the baroreflex-mediated, pressure-dependent control of heart rate. Hence, the action of anaesthetic agents on the cardiac vagus has two different aspects. They exert a central vagolytic action which is independent of arterial pressure and which determines heart rate. They also attenuate the pressure-dependent responsiveness of cardiac vagal tone and thereby the body's capability to stabilize reflexly its arterial pressure against challenges such as blood loss and orthostatic stress by the appropriate heart rate responses.

Although the neurophysiological evidence is lacking at present, it is presumably the central vagolytic action of anaesthetics that determines the heart rate response in other species. First, heart rate is dominated physiologically by vagal rather than sympathetic influences (Bishop, Peterson and Horwitz, 1976). Second, in animals, most i.v. anaesthetics inhibit efferent sympathetic drive which was demonstrated for thiopentone in man also (Wallin and König, 1976). Third, the heart rate responses to the agents studied correspond roughly with those found in other species. Whereas etomidate affects heart rate little in dogs as well as in man, the others elicit pronounced tachycardia in both species (Patschke et al., 1977; Arndt and Zindler, 1978). In non-premedicated man, for example, heart rate increases by 20 beat $\text{min}^{-1}$ or 30% on average for recommended clinical doses of barbiturates, Althesin and ketamine, and by 45 beat $\text{min}^{-1}$ after complete vagolysis with atropine 0.04 mg kg$^{-1}$ (Robinson et al., 1966). The estimate based on this comparison agrees fully with the neurophysiologically documented vagal inhibition in case of ketamine, but is smaller for Althesin and methohexitone. Yet, considering the dose-dependency of the heart rate effects (Patschke et al., 1977) and the problem of comparing equipotency of doses between species, not much emphasis can be put on these differences. It is presumably, therefore, the central vagolytic action which determines the heart rate response to these agents in man also.

The central inhibition of cardiac vagal neurones was demonstrated here neurophysiologically and found to be independent of baroreflex function and to differ in degree for equihypnotic doses of Althesin, methohexitone and ketamine. Etomidate had no consistent effect on cardiac vagal drive.

## REFERENCES

Arndt, J. O., Morgenstern, J., and Samodelov, L. (1977). The physiologically relevant information regarding systemic blood pressure encoded in the carotid sinus baroreceptor discharge pattern. *J. Physiol. (Lond.)*, **268**, 775.

—— Zindler, M. (1978). Effects of intravenous anesthetics on the circulation and its control; in *Hemodynamic Changes in Anesthesia*, Académie Europèene D'Anesthésiologie, The 5th European Congress of Anaesthesiology, Paris, vol. **3**, p. 1069.

Bishop, V. S., Peterson, D. F., and Horwitz, L. D. (1976). Factors influencing cardiac performance. *Int. Rev. Physiol.*, **9**, 239.

Bristow, J. D., Prys-Roberts, C., Fisher, A., Pickering, T. G., and Sleight, P. (1969). Effects of anesthesia on baroreflex control of heart rate in man. *Anesthesiology*, **31**, 422.

Davidson, N. S., Goldner, S., and McCloskey, D. I. (1976). Respiratory modulation of baroreceptor and chemoreceptor reflexes affecting heart rate and cardiac vagal efferent nerve activity. *J. Physiol. (Lond.)*, **259**, 523.

Fischer, K. (1973). Vergleichende tierexperimentelle Untersuchungen zum Einfluß verschiedener Narkotica auf das Herz; in *Ketamine—Neue Ergebnisse in Forschung und Klinik* (eds M. Gemperlem, D. Langrehr and H. Kreuscher), *Anaesth. Wiederbel.*, vol. **69**, p. 11. Berlin, Heidelberg, New York: Springer-Verlag.

—— Marquort, H. (1977). Experimental investigations on the direct effect of etomidate on myocardial contractility; in *Etomidate—An Intravenous Hypnotic Agent* (ed. A. Doenicke), *Anaesth. Wiederbel.*, vol. **106**, p. 95. Berlin, Heidelberg, New York: Springer-Verlag.

Hagenau, W., Pietsch, D., and Arndt, J. O. (1976). Der Effekt von Halothan und Enflurane sowie von Propanidid und Ketamin auf die Aktivität der Barorezeptoren des Aortenbogens decerebrierter Katzen. *Anaesthesist*, **25**, 331.

Hakumäki, M. O. K. (1972). Vagal and sympathetic efferent discharge in the Bainbridge reflex of dogs. *Acta Physiol. Scand.*, **85**, 414.

Katona, P. G., Poitras, J. W., Barnet, G. O., and Terry, B. S. (1970). Cardiac vagal efferent activity and heart period in the carotid sinus reflex. *Am. J. Physiol.*, **218**, 1030.

Inoue, K., Samodelov, L. F., and Arndt, J. O. (1980). Fentanyl activates a particular population of vagal efferents which are cardioinhibitory. *Naunyn Schmiedeberg's Arch. Pharmacol.*, **312**, 57.

Jewett, D. L. (1964). Activity of single efferent fibres in the cervical vagus nerve of the dog, with special reference to possible cardioinhibitory fibres. *J. Physiol. (Lond.)*, **175**, 321.

McGrath, J. C., MacKenzie, J. E., and Millar, R. A. (1975). Effects of ketamine on central sympathetic discharge and the baroreceptor reflex during mechanical ventilation. *Br. J. Anaesth.*, **47**, 1141.

MacKenzie, J. E., McGrath, J. C., Tetrault, J. P., and Millar, R. A. (1976). The effects of Althesin and thiopentone on sympathetic and baroreflex activity. *Can. Anaesth. Soc. J.*, **23**, 252.

Millar, R. A., Warden, J., Cooperman, L. H., and Price, H. L. (1970). Further studies of sympathetic actions of anaesthetics in intact and spinal animals. *Br. J. Anaesth.*, **42**, 366.

Morrison, J. L., Walker, H. A., and Richardson, A. P. (1950). The effect of pentobarbital on response of cardiovascular system of dogs to epinephrine, acetylcholine, and tilting. *Arch. Int. Pharmacodyn.*, **82**, 53.

Niederstrasser, D. (1981). Vergleich der Wirkung von Ketamin auf die Aktivität des Herzsympathikus, den arteriellen Blutdruck und die Herzfrequenz bei wachen und narkotisierten Hunden. Dissertation, Düsseldorf.

Patschke, D., Brückner, J. B., Gethmann, J. W., Tarnow, J., and Weymar, A. (1977). A comparison of the acute effects of intravenous induction agents (thiopentone, methohexitone, propanidid, Althesin, ketamine, piritramide and etomidate) on haemodynamics and myocardial oxygen consumption in dogs; in *Etomidate—An Intravenous Hypnotic Agent* (ed. A. Doenicke), *Anaesth. Wiederbel.*, vol. **106**, p. 49. Berlin, Heidelberg, New York: Springer-Verlag.

Reynolds, A. K., Chiz, J. F., and Pasquet, A. F. (1970). Halothane and methoxyflurane—A comparison of their effects on cardiac pacemaker fibers. *Anesthesiology*, **33**, 602.

Robinson, B. F., Epstein, S. E., Beiser, G. D., and Braunwald, E. (1966). Control of heart rate by the autonomic nervous system. *Circ. Res.*, **19**, 400.

Schumacher, I. G., and Arndt, J. O. (1978). Der Effekt von Methohexital, Fentanyl, Dehydrobenzperidol sowie von Chloralose auf die Aktivität der Barorezeptoren des Aortenbogens decerebrierter Katzen. *Anaesthesist*, **27**, 10.

Skovsted, P., Price, M. L., and Price, H. L. (1970). The effects of short-acting barbiturates on arterial pressure, preganglionic sympathetic activity and barostatic reflexes. *Anesthesiology*, **33**, 10.

—— Sapthavichaikul, S. (1977). The effects of etomidate on arterial pressure, pulse rate and preganglionic sympathetic activity in cats. *Can. Anaesth. Soc. J.*, **24**, 565.

Slogoff, S., and Allen, G. W. (1974). The role of baroreceptors in the cardiovascular response to ketamine. *Anesth. Analg. (Cleve.)*, **53**, 704.

Smith, N. T., and Corbascio, A. N. (1966). The cardiovascular effects of nitrous oxide during halothane anesthesia in the dog. *Anesthesiology*, **27**, 560.

—— Eger, E. I., II, Stoelting, R. K., Whayne, T. F., Cullen, D., and Kadis, L. B. (1970). The cardiovascular and sympathomimetic responses to the addition of nitrous oxide to halothane in man. *Anesthesiology*, **32**, 410.

Spyer, M. (1980). Neural organisation and control of baroreceptor reflex. *Rev. Physiol. Biochem. Pharmacol.*, **88**, 24.

Traber, D. L., Wilson, R. D., and Priano, L. L. (1970a). The effect of beta-adrenergic blockade on the cardiopulmonary response to ketamine. *Anesth. Analg. (Cleve.)*, 49, 604.

——————(1970b). A detailed study of the cardiopulmonary response to ketamine and its blockade by atropine. *South. Med. J.*, **63**, 1077.

Venes, J. L., Collins, W. F., and Taub, A. (1971). Nitrous oxide: an anesthetic for experiments in cats. *Am. J. Physiol.*, 220, 2028.

Wallin, B. G., and König, U. (1976). Changes of skin nerve sympathetic activity during induction of general anaesthesia with thiopentone in man. *Brain Res.*, **103**, 157.

## EFFERENTE VAGUSENTLADUNG UND HERZFREQUENZ NACH METHOHEXITAL, ALTHESIN, KETAMIN UND ETOMIDATE BEI KATZEN

### ZUSAMMENFASSUNG

Die chronotropen Effekte von Methohexital, Althesin, Ketamin und Etomidate auf die Entladung einer Faser des efferenten Herzvagus und auf die Herzfrequenz wurde an Katzen untersucht. Der efferente Herzvagus wurde ausgeprägt und regelmäßig durch äquipotene Dosen von Methohexital (5,0 mg kg$^{-1}$) Althesin (0,1 ml kg$^{-1}$) und Ketamin (5,0 mg kg$^{-1}$), aber nicht durch Etomidate (0,8 mg kg$^{-1}$) inhibiert. Diese inhibitorischen Effekte waren unabhängig vom arteriellen Druck und spiegelten den Anstieg der Herzfrequenz, die durch die ersten drei Substanzen ausgelöst worden war, wieder. Etomidate beeinflußte weder die Entladung des Herzvagus noch die Herzfrequenz. So inhibieren also Metohexital, Althesin und Ketamin den efferenten Herzvagus durch ihre zentrale Wirkung unabhängig von der Funktion der Baroreflex-Funktion. Diese zentrale Vagolyse ist wahrscheinlich die Ursache ihres positiven chronotropen Effektes.

## RESPONSE VAGALE EFFERENTE ET FREQUENCE CARDIAQUE APRES INJECTION DE METHOHEXITONE, D'ALTHESIN, DE KETAMINE ET D'ETOMIDATE CHEZ LE CHAT.

### RESUME

Nous avons étudie les effets chronotropes de la methohexitone, de l'Althésin, de la kétamine et de l'etomidate sur la décharge d'une fibre unique des efférents cardiaques vagaux et sur la fréquence cardiaque chez le chat. Les efférents cardiaques vagaux étaient inhibés de façon marquée et reproductible pour des doses équihypnotiques de méthohéxitone (2,0 mg kg$^{-1}$) d'Althésin (0,1 ml kg$^{-1}$) et de kétamine (5,0 mg kg$^{-1}$) mais pas d'étomidate (0,8 mg kg$^{-1}$). Ces effets inhibiteurs étaient indépendants de la pression artérielle et reflétaient les augmentations de fréquence cardiaque induites par les trois premiers agents. L'étomidate n'avait régulièrement pas d'effets sur la décharge cardiaque vagale ou la fréquence cardiaque. Ainsi la méthohexitone, l'Althésin et la kétamine inhibent la transmission vagale cardiaque efférente par leur action centrale indépendemment du baroréflexe. Cette vagolyse centrale est probablement la cause de leurs effets chronotropes positifs.

## DESCARGA VAGAL EFERENTE Y RITMO CARDÍACO EN RESPUESTA A METOHEXITONA, ALTESINA, QUETAMINA Y ETOMIDATO EN LOS GATOS

### SUMARIO

Se llevaron a cabo estudios sobre los efectos cronotrópicos de la metohexitona, la altesina, la quetamina y el etomidato en la descarga de fibra única de los eferentes vagales cardíacos y en el ritmo cardíaco. Los eferentes vagales cardíacos fueron inhibidos de manera marcada y regular por dosis equihipnóticas de metohexitona (2,0 mg kg$^{-1}$), de Altesina (0,1 ml/kg$^{-1}$) y de quetamina (5,0 mg/kg$^{-}$), perono fue asi por las de etomidato (0,8 mg/kg$^{-1}$). Dichos efectos inhibitorios fueron independientes de la presión arterial y reflejaron los aumentos del ritmo cardíaco producidos por los tres primeros agentes. El etomidato no afectó la descarga vagal cardíaca ni tampoco el ritmo cardíaco, y eso de manera uniforme y constante. Entonces, la metohexitona, la Altesina y la quetamina inhiben el impulso vagal cardíaco eferente por su acción central, independientemente de la función de baroreflejo. Esta vagólisis central constituye probablemente la causa de sus efectos cronotrópicos positivos.

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# DURAL PERMEABILITY TO NARCOTICS: *IN VITRO* DETERMINATION AND APPLICATION TO EXTRADURAL ADMINISTRATION

R. A. MOORE, R. E. S. BULLINGHAM, H. J. MCQUAY, C. W. HAND, J. B. ASPEL, M. C. ALLEN AND D. THOMAS

## SUMMARY

The permeability of cranial and lumbar dura to various substances including a number of narcotic analgesics was measured *in vitro*. Preliminary data on human postmortem material is reported. Permeability had a linear relation to the inverse of the square root of molecular weight. This is the expected relationship for a diffusion process dependent upon molecular weight. The differential mass selectivity coefficients for lumbar and cranial dura were calculated; they were similar at 0.8 and 0.9. This was greater than for diffusion in simple liquids, but much less than that for biological lipid membranes. This suggests that the low rates of diffusion are a property of the thickness of the dura rather than any inherent impermeability. A simple model for the dural transfer of drugs is described, and applied to narcotics. Its purposes were to suggest: the factors involved in the dural transfer of drugs; the physicochemical properties of drugs relevant to their dural transfer; worthwhile measurements in future studies. The model indicates that drug molecular weight and rate of absorption are important determinants of the efficiency of dural transfer. Low molecular weight and slow absorption produce high dural transfers. When applied to narcotics, these factors could produce a difference of up to an order of magnitude in the amount transferred directly across the dura.

The presence of opiate receptors in the spinal cord was the basis for the spinal (intrathecal and extradural) use of narcotics. Animal studies (Yaksh and Rudy, 1976; Yaksh et al., 1980), confirmed in man, show that analgesia (Wang, Nauss and Thomas, 1979; Magora et al., 1980), hormonal (Cowen et al., 1982) and side-effects (Reiz and Westberg, 1980) occur after spinal use. The nature and frequency of these effects indicate that spinal opiates do have specific regional activity.

There are more reports of extradural opiate use than of intrathecal use. The fate of drugs given extradurally is complicated (Bromage, 1975, 1981). The desired direct transfer of narcotic across the dura competes with uptake and removal by the extensive extradural venous blood flow and with reversible uptake into extradural adipose tissue. While local actions of narcotics outside the central nervous system (c.n.s.) have been described (Sastry, 1979; Mays et al., 1981), it is generally accepted that their principal actions are within the c.n.s. This is a critical difference from the extradural use of local anaesthetics.

The systemic availability of extradurally administered narcotics resembles that of the same dose given i.m. (Cousins et al., 1979; Weddel and Ritter, 1981). How much of this extradural narcotic is transferred directly across the dura? The magnitude of this transfer will determine the additional regional effect from extradural administration, and it is this additional regional effect which justifies the use of the procedurally elaborate extradural route for opiates.

In the first part of this study rates of transfer of a variety of compounds across human cranial and lumbar dural membranes were measured *in vitro*. The experimental aims were to obtain: physicochemical data on the nature of the dural membrane; an order of magnitude estimate for the transfer rates of narcotic drugs across the dura; and an estimate of the relative transfer rates that can be expected for different narcotics.

The second part of the paper presents a simple model which describes dural drug transfer. The

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model is semiquantitative, allows discussion of the qualitative factors involved and is applied to extradural narcotics. Using *in vitro* data on dural permeability obtained experimentally, it provides a rational basis for choice of drug and of injection volume. Appropriate measurements are suggested which may be helpful in assessing the efficiency of dural transmission in pharmacokinetic terms. In particular, the model suggests reasons why the degree of dural transmission may vary between individuals. This variation may contribute to the wide range of analgesic effect which is such a feature of the clinical use of extradural narcotics.

## METHODS

An apparatus suitable for the study of the transfer of compounds across the dura mater was designed and built in the Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford. It consisted of two Perspex blocks each with a chamber of similar shape and volume (10 ml) which clamped together so that the chambers communicated through a port of fixed area (2.83 $cm^2$). The whole device was kept at a given temperature using a temperature-controlled water bath (fig. 1).

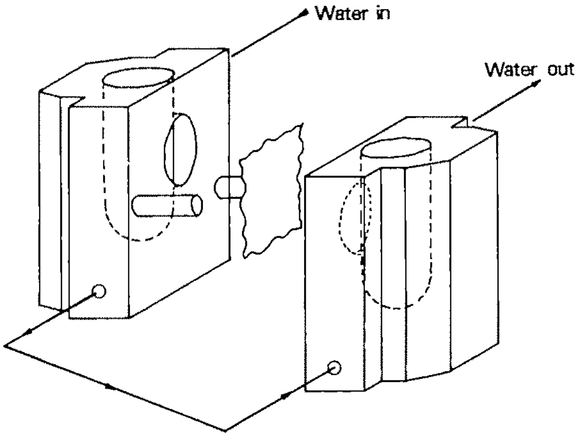

FIG. 1. Apparatus used for dural transfer experiments.

The dura used in these experiments was obtained at postmortem from subjects with no history of neurological disorder and in whom there was no reason to suspect damage to the dural membranes. The specimens were washed to remove any blood and then frozen until required. Pieces of dura, both cranial and lumbar, were then cut to a size of approximately 4 $cm^2$ and placed over the port of one of the blocks. The other block was then screwed tightly into place by means of four locating screws. The chambers were filled with a quantity of Tris buffer (Tris-Cl 0.2 mol $litre^{-1}$, pH 7.4 at 37 °C).

The chambers always contained a final volume of 10 ml. The contents of the chambers were stirred throughout by means of a magnetic follower in each chamber. The apparatus was allowed to reach the required temperature before the experiment was started. An exact volume of a solution of the compound under test was then introduced to chamber 1 of the apparatus and immediately a sample (100 μlitre) was removed from chamber 2 at time 0. Further samples, again of 100 μlitre (to a total volume of 600 μlitre out of 10 ml without replenishment with buffer) were taken from chamber 2 at 5-min intervals up to 25 min. The apparatus was washed thoroughly with Tris buffer between experiments.

A wide variety of compounds was studied: methanol, ethanol and propanol were measured by gas–liquid chromatography (Curry, Walker and Simpson, 1966); digoxin by radioimmunoassay using a kit obtained from Amersham International; glucose by an enzymatic glucose oxidase technique using a Beckman analyser; cortisol by competitive protein binding (Beardwell, Burke and Cope, 1968); fentanyl by radioimmunoassay using a kit obtained from IRE (UK) Ltd; morphine and diamorphine by radioimmunoassay using an antiserum from Guildhay antisera which cross-reacted with both drugs; methadone by radioimmunoassay using a label from Research Triangle Institute, a gift from the National Institute for Drug Abuse, and antiserum which was a gift from Prof. C. Inturissi; buprenorphine by radioimmunoassay (Bartlett et al., 1980); progesterone by radioimmunoassay using antisera obtained from Guildhay antisera and phenazocine by measuring its fluorescence in HCl 1 mol $litre^{-1}$ at an excitation wavelength of 284 nm and an emission wavelength of 310 nm.

Initial experiments used cranial dura from four individuals, and examined the variation in permeability of the dura to ethanol at different concentrations and temperatures. Further experiments examined the permeability of both cranial and lumbar dura obtained from a single individual to a variety of compounds. Three pieces of cranial dura (both meningeal and endosteal layers) were used, but only one piece of lumbar dura (just the meningeal layer) was available.

Initial concentrations of compound under study were chosen to provide samples in the measurable range for each assay. The initial concentrations used were 10% (v/v) for the aliphatic alcohols, 100 $\mu$mol litre$^{-1}$ for the steroids and 0.1 mg ml$^{-1}$ for all the drugs except digoxin, for which the initial concentration was 0.01 mg ml$^{-1}$. These are comparable to reported initial concentrations for extradural narcotics varying from 10 mg ml$^{-1}$ for pethidine (Cousins et al., 1979) to 0.015 mg ml$^{-1}$ for fentanyl (Bullingham, McQuay and Moore, 1980). All experiments were performed in duplicate.

*Calculation of permeability*

The method of analysis was based on the Fick law of diffusion which states that diffusion flux is proportional to the concentration gradient.

$$\text{Flux} = \frac{\text{constant} \times \text{area} \times \text{concentration gradient}}{\text{thickness}}$$

$$\dot{Q} = \frac{K \times A \times C_1 - C_2}{d}$$

where $K$ = constant
$A$ = area
$C_1$ = concentration in chamber 1
$C_2$ = concentration in chamber 2
$d$ = thickness of dura.

In this experiment the concentration decrease in chamber 1 during the experiment was very small (in the worst case less than 2%). Thus the concentration gradient was equivalent to the initial concentration in chamber 1, and did not alter during the experiment.

$$\dot{Q} = \frac{K \times A \times C_1}{d}$$

The thickness, $d$, cannot be known with certainty, but is constant for a given piece of dura. A new constant, the permeability $P$, can now be defined:

$$P = \frac{K}{d}$$

Thus

$$\dot{Q} = P \times A \times C_1$$

or

$$P = \frac{\dot{Q}}{A \times C_1}$$

The total amount of substance which appeared in chamber 2 at each interval was plotted against time. The slope of this graph represents the flux of a compound through a given area of dura. Division by the area of the port (2.83 cm$^2$) and the initial concentration in chamber 1 ($C_1$) yields a value for the permeability.

$$\text{Now} \quad P = \frac{\text{slope}}{2.83 C_1}$$

This has the units of cm min$^{-1}$.

The thickness of the specimens of dura was measured at several separate sites with a micrometer. The nature of the material made such measurements only approximate.

## RESULTS

In all experiments with all compounds tested on both lumbar and cranial dura, the appearance of substances in the low concentration side of the apparatus (chamber 2) was linear with respect to time, with correlation coefficients generally in excess of 0.98 for seven data points.

The experiments used either single pieces of dura from different subjects (tables I, II) or different

TABLE I. *Effect of concentration on the permeability of cranial dura to ethanol. Experiments carried out in duplicate at 37 °C on cranial dura from four subjects. Results are mean ± SD. *Significant difference from 0.12 mol litre$^{-1}$ ($P < 0.05$, one-tailed Student's t test)*

| Ethanol concentration (mol litre$^{-1}$) | Permeability (cm min$^{-1}$) |
|---|---|
| 0.12 | 0.0048 ± 0.0010 |
| 0.24 | 0.0048 ± 0.0010 |
| 0.59 | 0.0048 ± 0.0009 |
| 1.15 | 0.0044 ± 0.0002 |
| 1.69 | 0.0040 ± 0.0004 |
| 2.20 | 0.0033 ± 0.0004* |

TABLE II. *Effect of temperature on the permeability of cranial dura to ethanol. Experiments carried out in duplicate at 0.59 mol litre$^{-1}$ ethanol using cranial dura from three subjects. Results are mean ± SD. *Significant difference from 37 °C value ($P < 0.01$, one-tailed Student's t test)*

| Temperature (°C) | Permeability (cm min$^{-1}$) |
|---|---|
| 25 | 0.0050 ± 0.0002* |
| 30 | 0.0053 ± 0.0002* |
| 35 | 0.0061 ± 0.0001 |
| 37 | 0.0063 ± 0.0002 |
| 40 | 0.0069 ± 0.0002* |
| 45 | 0.0074 ± 0.0001* |

pieces of dura from the same subject (table III). The dispersion of the data was similar in each case, with an overall coefficient of variation of 8.7±2.2% (SEM) in the former, and 12.5±2.7% in the latter experiments. The experimental error was not significantly different for either type of experiment.

The dural permeabilities for experiments on cranial dura with varying ethanol concentration or temperature are shown in tables I and II. The permeability declined as the initial ethanol concentration increased to more than 0.6 mol litre$^{-1}$; this became statistically significant only when the initial concentration was 2.2 mol litre$^{-1}$. Permeability increased with temperature (table II); at 30 °C or less the values were significantly less than at 37 °C, and were significantly greater at temperatures of 40 °C or more.

Permeability of both cranial and lumbar dura to a variety of compounds is shown in table III. The results are displayed graphically in figure 2, where permeability plotted against 1/(square root of molecular weight) produced a straight line relationship with a correlation coefficient of 0.97 for both cranial and lumbar dura. This is the expected relationship for a diffusion process dependent upon molecular weight. The permeability of lumbar dura was significantly greater than that of cranial dura by about 30% ($P<0.05$, paired *t* test). The thickness of cranial dura was about 0.5 mm and that of lumbar dura about 0.3 mm.

Fentanyl was excluded from the calculations, and from those for linear regression against molecular weight. Fentanyl had a permeability which, particularly for cranial dura, was about three times greater than expected for that molecular weight, with careful checking of the results and repetition of the experiment.

## DISCUSSION OF EXPERIMENTAL RESULTS

Initial experiments on the permeability to ethanol of cranial dura from several subjects demonstrated that it was a saturable phenomenon (table I). When the initial concentration of ethanol increased to 2.2 mol litre$^{-1}$ the permeability was significantly reduced. This concentration is at least an order of magnitude greater than that likely to be found in the extradural use of narcotics. Typically, concentrations used are about 50 mmol litre$^{-1}$ for pethidine (Cousins et al., 1979) and 45 μmol litre$^{-1}$ for fentanyl (Bullingham et al., 1980). The permeability was also affected by temperature; there was an increase of 50% when the temperature increased from 25 to 45 °C (table II), which is consistent with a diffusion basis for the permeability.

The absolute permeabilities of compounds across both cranial and lumbar dura were low, but were of the order of 0.0015 cm min$^{-1}$ for compounds with molecular weights typical of opiate drugs. The permeability of the same compounds across the lumbar dura was generally similar to and usually greater than that for cranial dura (table III), which accords with the greater thickness of cranial dura. Excluding

TABLE III. *Dural permeability for various compounds. The results on any piece of dura are the mean of duplicate experiments. For cranial dura where experiments were performed on three different pieces the results are mean ± SD except where* n *= 1 (*). The molecular weights given are for the free compound. NR = no result available*

| | | Permeability (cm min$^{-1}$) | | |
|---|---|---|---|---|
| Compound | MW | Cranial dura | Lumbar dura | Lumbar/cranial |
| Methanol | 32 | 0.0060±0.0005 | 0.0099 | 1.64 |
| Ethanol | 46 | 0.0059±0.0006 | 0.0076 | 1.28 |
| Propanol | 60 | 0.0039±0.0008 | 0.0063 | 1.59 |
| Glucose | 180 | 0.0025±0.0003 | NR | NR |
| Morphine | 285 | 0.0015±0.0001 | 0.0036 | 2.36 |
| Methadone | 310 | 0.0012* | 0.0014 | 1.16 |
| Progesterone | 315 | 0.0012±0.0001 | 0.0011 | 0.96 |
| Phenazocine | 322 | 0.0015* | NR | NR |
| Diamorphine | 326 | 0.0014* | NR | NR |
| Fentanyl | 337 | 0.0061±0.0017 | 0.0048 | 0.80 |
| Cortisol | 363 | 0.0016±0.0001 | 0.0019 | 1.18 |
| Buprenorphine | 468 | NR | 0.0004 | NR |
| Digoxin | 781 | 0.0003* | 0.0005 | 1.73 |

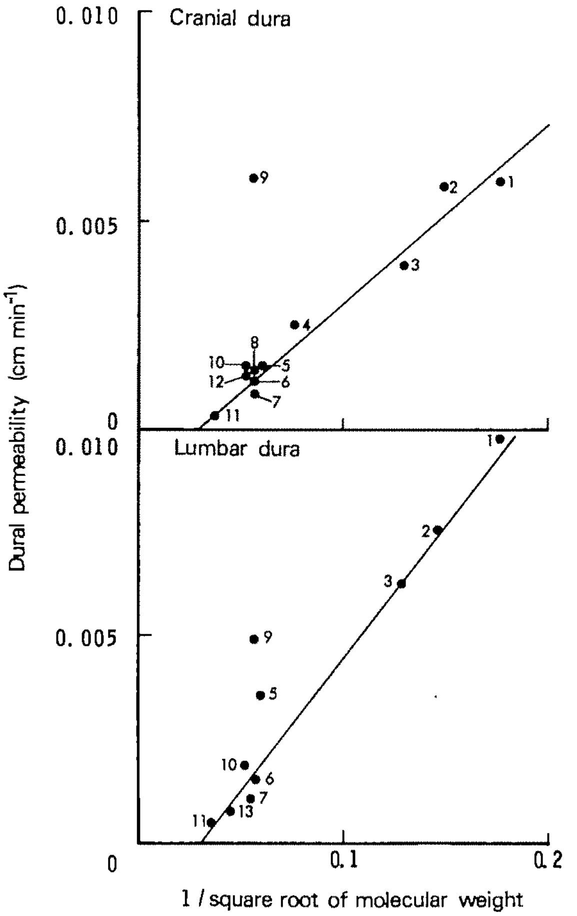

FIG. 2. Relationship between permeability and reciprocal of the square root of molecular weight. The compounds were: 1 = methanol; 2 = ethanol; 3 = propanol; 4 = glucose; 5 = morphine; 6 = methadone; 7 = progesterone; 8 = phenazocine; 9 = fentanyl; 10 = cortisol; 11 = digoxin; 12 = diamorphine; 13 = buprenorphine. The equations for the regression lines with fentanyl excluded were: cranial dura: $y = 0.041x - 0.001$ ($r = 0.983$, $P < 0.01$, $n = 10$); lumbar dura: $y = 0.065x - 0.002$ ($r = 0.978$, $P < 0.01$, $n = 9$).

fentanyl, which displayed aberrant behaviour, the trend was statistically significant.

There was a marked relationship between permeability of all the compounds tested and molecular weight (fig. 2). This relationship was seen over a wide range of molecular weights, from methanol (32 daltons) to digoxin (781 daltons). Lipophilicity was apparently not an important factor, as can be seen from the fact that morphine and diamorphine, which have very different lipid solubilities yielded similar permeabilities.

An exception to the general rule for molecular weight was fentanyl, which crossed cranial and lumbar dura faster than would be predicted from its molecular weight. The reasons for this are not clear. Fentanyl is a lipophilic basic opiate, essentially similar in terms of its lipophilicity and $pK_a$ values to some of the other opiates tested in this system. However, Lieb and Stein (1969) in their investigation of the behaviour of compounds in biological membranes, noted that some compounds (particularly trimethylcitrate) behaved in a similarly anomalous manner. They suggested that the relationship was more properly between diffusion rate and molecular volume rather than molecular weight. Most of the compounds tested have a shape which approximates to a sphere; fentanyl, in contrast, is an extended molecule. The enhanced permeability found with fentanyl may also apply to molecules with similar structures, such as phenoperidine. In addition, the discovery that fentanyl has aberrant behaviour in dural transfer experiments, without being able to explain that behaviour, implies that it would be worthwhile to investigate all opiate drugs for special dural permeability.

Lieb and Stein defined a parameter, the differential mass selectivity coefficient ($s_m$), which is a constant characteristic of a membrane at a given temperature and describes numerically the property of any material for impeding diffusion. The value of $s_m$ is independent of thickness, and was obtained for dura by plotting the $\log_{10}$ permeability against $\log_{10}$ molecular weight relative to methanol. The $s_m$ value was the negative of the slope.

The values for lumbar and cranial dura obtained by this type of plot (fig. 3) were very similar at 0.8 and 0.9. This is interesting for two reasons. First, as lumbar and cranial dura have the same anatomical and biochemical structure, the values for $s_m$ should be identical; the fact that this result was obtained gives confidence in the experimental data. Second, the value obtained in these experiments was greater than that for diffusion in simple liquids (0.3–0.5), but much less than those calculated by Lieb and Stein for biological cell membranes (2.9–6.0), or for polymethyl acrylate (3.8) or natural rubber (1.1). The collagen and elastin fibres of dura form a much more open structure than a lipid cell membrane. However, the cranial dura was about 0.5 mm thick, and lumbar dura about 0.3 mm; this is much greater than for lipid membranes. The apparent low permeability of dura is then almost entirely a product of

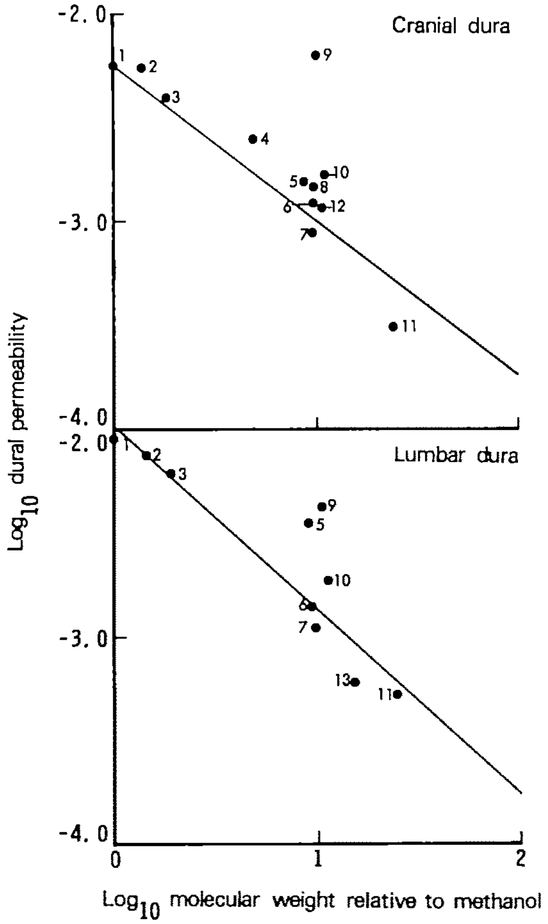

FIG. 3. Relationship between $\log_{10}$ permeability and $\log_{10}$ molecular weight relative to methanol. The differential mass selectivity coefficient, $s_m$, is the negative of the slope. Compounds were as for figure 2. The equations to the regression lines with fentanyl excluded were — cranial dura: $y = -0.80x - 2.11$ ($r = 0.933$, $p < 0.01$, $n = 11$); lumbar dura: $y = -0.91x - 1.95$ ($r = 0.917$, $P < 0.01$, $n = 9$).

its considerable thickness rather than any specific impermeability.

The dura used in these latter experiments came from a single subject. Further work will be required to widen these results to dural specimens from other subjects. The evidence here of experimental variation for a single or several dural specimens suggests that extension of the experiments would not grossly alter the estimates of narcotic permeability or their relative order.

### A MODEL FOR THE PREDICTION OF THE FRACTION OF AN EXTRADURAL DOSE WHICH IS TRANSFERRED DIRECTLY ACROSS THE DURA

Transfer of drug across the dura will be assumed to follow Fick's law of diffusion, as was found for *in vitro* dural samples experimentally.

It is assumed (all assumptions are examined for validity below):

(i) the dura has uniform thickness and diffusion properties;

(ii) intradural (c.s.f. and cord) drug concentration is at all times close to zero. Intradural drug concentration is then neglected with respect to extradural drug concentration, so that the concentration gradient for diffusion across the dura is determined solely by extradural drug concentration.

The mass flux of drug across the dura (mass per minute) is then:

$$\frac{dQ}{dt} = P \times A \times C_{ex} \qquad (1)$$

where

$Q$ = quantity transferred (mass units)

$P$ = dural permeability (cm $\text{min}^{-1}$). (This term includes the thickness of the dura and corresponds to the values determined experimentally *in vitro*.)

$A$ = area of dura exposed to the drug ($\text{cm}^2$)

$C_{ex}$ = extradural drug concentration (mass per ml). (The relevant drug fraction is that which is unbound.)

$t$ = time (min)

Systemic availability after extradural opiate use resembles that seen after i.m. absorption. The amount of drug remaining at the extradural site of administration may be represented by a first order rate process, giving:

$$D_{ex} = D_0 \times \exp -(k_{abs} \times t)$$

where:

$D_{ex}$ = dose of drug remaining at the extradural site of deposition (mass units) after time $t$ (min)

$D_0$ = the initial extradural dose (mass units)

$k_{abs}$ = the absorption rate constant ($\text{min}^{-1}$)

Assuming also:

(iii) the relationship between extradural drug dose and extradural drug concentration is described by:

$$C_{ex} = \frac{D_{ex}}{V_{ex}}$$

where:

$C_{ex}$ = extradural drug concentration
$V_{ex}$ = an extradural volume of distribution (ml). (In general, this volume could include such effects as binding and ionization of the drug.)

Then:

$$C_{ex} = \frac{D_0}{V_{ex}} \times \exp -(k_{abs} \times t)$$

Substituting this into equation (1), integrating over all time, and assuming:

(iv) $V_{ex}$ is not a function of time

then:

Total fraction of drug transferred directly across the dura,

$$F_D = \frac{Q}{D_0}$$

$$= P \times A \times \frac{1}{V_{ex}} \times \int_0^{\alpha} \exp -(k_{abs} \times t)\, dt$$

$$= \frac{P}{k_{abs}} \times \frac{A}{V_{ex}} \qquad (2)$$

## General features of the model

Note first that equation (2) separates into two terms:

(a) $P/K_{abs}$: a ratio of rate factors for which the *drug* is a major determinant.

(b) $A/V_{ex}$: a ratio of geometric factors for which the details of technique and the anatomy of the extradural space are major determinants, that is this is *situation* dependent.

Consider now the separate factors with the two terms:

### *(a) Drug-dependent terms*

*Dural permeability, P*

High permeability gives high total transfers. Permeability is determined by:

*Molecular weight (MW).* Increase in MW is a principal factor for decrease in permeability. Most of the commonly used opiates have very similar MW in the range 300–400 daltons. Lower MW opiates include morphine (MW 285), levorphanol (MW 257), and meperidine (MW 246.5).

*Molecular shape.* The dura may be much more permeable to extended molecules than to globular molecules of the same MW. Thus fentanyl (MW 336) shows an anomalously high permeability in comparison with phenazocine (MW 321) or even morphine (MW 285). Molecular shape may be a very significant property for high permeability.

*Lipophilicity.* Increase in lipophilicity should increase permeability for a given MW. This increase usually involves the attachment of large hydrophobic residues to a molecule. The concomitant increase in MW may offset the effect of increase in lipophilicity. Thus diacetylmorphine (MW 369) is much more lipophilic than morphine (MW 285) but still has a lower permeability.

*Degree of ionization.* Penetration of lipid barriers can only be achieved by un-ionized drug molecules.

$$\mathrm{pH} = \mathrm{p}K_a + \log_{10}\frac{\text{(concentration of protonated base)}}{\text{(concentration of free base)}}$$

The narcotic solutions reported for extradural use have used dextrose or saline solutions and hence had minimal buffering capacity. The pH of these solutions should therefore have come rapidly to that of the extradural space (assumed to be approximately 7.4).

The apparent p$K_a$ of the common narcotics (Benson, Kaufman and Koski, 1976) are in the range 7–10. Thus at pH 7.4, the major fraction of such narcotics will be in the ionized form. Change in the degree of ionization is most rapid at pH values close to the p$K_a$. The effect of p$K_a$ on permeability would then be greater with narcotics with p$K_a$ values at the lower end of the range such as morphine (Benson, Kaufman and Koski, 1976), p$K_a$ = 7.93, and meperidine (Benson, Kaufman and Koski, 1976) p$K_a$ = 8.50.

The dural membrane is not primarily a lipid barrier like the cell membrane. Taken with the discussion of narcotic ionization above, this means that p$K_a$ is likely to be of only minor significance for permeability.

*The absorption rate constant $k_{abs}$*

Low absorption rate constants (slow appearance in the systemic circulation) will give high total dural transfers. In essence, the extradural drug concentration is maintained for longer. The absorption rate constant is determined by:

*Lipophilicity.* Increase in lipophilicity could lead to two opposing effects:

(i) A more rapid transfer into blood and thus an increase in $k_{abs}$. This is the general correlation seen for the i.m. use of opiates (Bullingham, 1981).

(ii) Increase in non-specific binding (Hollt and Teschemacher, 1975). Uptake into extradural adipose tissue will reduce the concentration gradient for diffusion into the vascular system, and hence reduce $k_{abs}$.

The overall effect of lipophilicity could consequently be small. The presence of extradural adipose tissue is a cardinal distinction between this site and muscle. Moreover, the quantity of adipose tissue in the extradural space is likely to vary between patients. Even within the same patient it may vary in relation for example to age or diet.

This leads to difficulties in predicting the effect of lipophilicity on $k_{abs}$. It may, however, be determined pharmacokinetically in the clinical situation, which should resolve the relative importance of each of the above competing processes. The small difference between i.m. and extradural absorptions reported for meperidine and morphine suggests that the non-specific binding effect is of only minor significance. Increase in lipophilicity leads then to increase in $k_{abs}$ as with intramuscular use.

*Extradural blood flow.* High extradural blood flow removes extradural drug more rapidly and so increases $k_{abs}$. Two examples are:

(i) Pregnancy (or other large intra-abdominal tumour) increases extradural blood flow.

(ii) Extradural vasoconstrictors (e.g. adrenaline) are expected to reduce extradural blood flow. The end result of using vasoconstrictors may not, however, be straightforward. Drugs of low lipophilicity, such as morphine, already have a relatively small $k_{abs}$; a vasoconstrictor may then exert only a small additional effect. With highly lipophilic drugs, transfer of drug into fat may already be exerting a significant reduction in $k_{abs}$ which will outweigh the effect of a vasoconstrictor. Very significant effects may only be seen with vasoconstrictors when very lipophilic drugs are used in patients who have little extradural fat and high extradural blood flows.

### *(b) Situation-dependent terms*

*Dural surface exposed to drug, A*

High surface areas give high total dural transfers. The principles which underly the extent of spread of extradurally administered solutions are reasonably well understood (Atkinson, Rushman and Lee, 1977). Information established for local anaesthetics is here equally applicable to other extradural drugs. The principal determinant is the volume of injectate. Other factors include posture and patient-related variables such as age and height. One notable difference between extradural narcotics and local anaesthetics concerns the level at which the spinal theca ends (commonly taken as S2). Any narcotic placed below this level may be regarded as lost to direct dural transfer. There is little logic in the sacral administration of narcotics.

*Volume of distribution of extradural drug, $V_{ex}$*

Small volumes give high total dural transfers. $V_{ex}$ is an apparently simple factor, but is determined by a number of very complicated events.

The volume of distribution is certainly related to the volume of injectate: larger injectate volumes will give larger volumes of distribution. Large injectate volumes will also increase the dural area ($A$) exposed to drug, so that, within limits, the opposed effects of these two factors may be expected to cancel. This implies a certain degree of independence of the extent of dural transfer from the volume of extradural solution given. A similarity may be noted here with extradural use of local anaesthetics with which, above a certain concentration of the local anaesthetic, the effect is observed to be independent of volume of injectate (Bromage, 1975).

Local anaesthetics, however, also act on nerve bundles within the extradural space. Extradural narcotics must enter the neuraxis for their major effects. This difference means that $V_{ex}$ may play a more fundamental role in the case of extradural narcotics and this is discussed below.

## AN ESTIMATION OF THE FRACTION OF AN EXTRADURAL NARCOTIC DOSE TRANSFERRED DIRECTLY ACROSS THE DURA

Morphine and buprenorphine have been chosen as examples because they represent extremes for lipophilicity and MW (table I). To estimate $F_D$ in equation (2), numerical values must be assigned to the parameters contained within it:

*Permeability, P*

The values used are those measured on a sample of human lumbar dura *in vitro*, as described earlier.

*Absorption rate constant, $k_{abs}$*

The plasma profile of morphine after extradural administration resembles that of an i.m. administration (Weddel and Ritter, 1981). The values used are those reported for i.m. morphine in five volunteers (Stanski, Greenblatt and Lowenstein, 1978).

Both i.m. (Bullingham et al., 1980) and extradural (Bullingham, McQuay and Moore, 1980) buprenorphine show very rapid systemic absorption. I.m. buprenorphine produced peak concentrations within 5 min of administration. Using the terminal half-life of buprenorphine, 300 min (Bullingham et al., 1982), an estimate for the absorption half-life of 0.55 min may be obtained. A range of 0.1–1.0 is also taken around this value.

*Dural surface exposed to drug,* A

In the adult (Collins, 1976) the weight of the spinal cord is about 30 g, and so its total volume will be about 30 ml. The total volume of c.s.f. in the spinal subarachnoid space is 25–30 ml. The combined volume of c.s.f. and cord is thus about 60 ml, and spans 25 vertebral segments, from the foramen magnum to S2, over a vertical distance of about 50 cm. The volume per vertebral segment is thus about 2.4 ml in a vertical height of 2.0 cm. This volume can be considered as a uniform right cylinder with dura covering the curved surface. Its radius, $r$, is given by:

$$\pi \times r^2 \times 2.0 = 2.4$$

that is, $r = 0.62$ cm

The dural surface area per vertebral segment is then:

$$2 \times \pi \times r \times 2.0 = 7.77\ \text{cm}^2$$

The usual volume of injectate for extradural narcotics has been 10 ml, given at L2/3. This spreads 6–8 vertebral segments, that is it covers an area of 46.6–62.1 cm$^2$. In all the calculations $A$ has therefore been assigned a value of 50 cm$^2$.

*Volume of distribution of extradural drug, $V_{ex}$*

No value can be assigned to this parameter to represent the clinical situation. However, it is instructive if $V_{ex}$ is given the volume of injectate—10 ml. This model of the clinical administration then corresponds to the experimental design used for the earlier *in vitro* determination of dural permeabilities.

The fraction of extradural dose transferred directly across the dura, calculated using equation (2) and the above values, is shown in table IV.

These calculations indicate:

(a) the possibility of a wide range of efficiency of dural transfer, depending on the drug used,
(b) the potential for surprisingly high efficiencies of dural transfer, and
(c) the deleterious effect of increase in drug MW and lipophilicity on dural transfer.

Of the assumptions used in these calculations, the least valid is that for $V_{ex}$. This factor now becomes central to realistic estimates of dural transfer.

*The nature of $V_{ex}$.* In this model, $V_{ex}$ represents that volume where extradural drug is distributed,

TABLE IV. *Comparison of calculated dural transfer for morphine and buprenorphine (range). *Lipophilicity is expressed as $\log_{10}$ (partition coefficient). The partition coefficients are those reported between heptane/water at a buffered pH of 7.4 (Kutter, Herz and Teschemacher, 1970; Kosterlitz, Leslie and Waterfield, 1975). † All values are taken from experimental data obtained previously. ‡ Half-life of absorption, $T_{\frac{1}{2}abs}$ and $k_{abs}$ are related by $k_{abs} = \log_e 2/(T_{\frac{1}{2}abs})$. § Calculated using equation (2) as $F_D \times 100$. Injected volume $V_{ex} = 10$ ml, giving $A = 50$ cm$^2$*

| | Morphine | Buprenorphine |
|---|---|---|
| Molecular weight | 285 | 467 |
| Lipophilicity* | −5.0 | 1.78 |
| Permeability† | | |
| $P$ (cm min$^{-1}$) | 0.0036 | 0.00043 |
| Half-life of absorption | | |
| $T_{\frac{1}{2}}$ (min) | 7.7 | 0.55 |
| | (3.1–11.5) | (0.1–1.0) |
| Absorption rate constant‡ | | |
| $k_{abs}$ (min$^{-1}$) | (0.224–0.060) | (6.93–0.693) |
| % of extradural dose | | |
| Transferred across dura§ | 20.0 | 0.17 |
| | (8.1–30.0) | (0.03–0.3) |

such that it is effectively available for transfer across the dura.

Consider the calculations in table IV. The value assigned to $V_{ex}$ was that of the volume of injectate. This is the analogy of the *in vitro* situation, where the drug solution is well-stirred and where none of the drug is bound. All of the remaining drug is available all of the time to the dural surface, *A*.

Now consider the real situation after extradural drug administration *in vivo*:

(i) The volume into which the drug disperses is certainly not well-stirred. Dural transfer, blood removal and fat uptake will produce local concentration gradients within the volume.

Consider the case of morphine. Its low lipophilicity will give relatively low rates of blood removal and fat uptake; its low MW gives a relatively rapid dural transfer. A zone of drug depletion will occur around the immediate vicinity of the dura. Although drug can diffuse in to replenish this zone, diffusion is a slow process. By comparison with the well-stirred equivalent, this appears as a reduction in peridural drug concentration, that is an increase in $V_{ex}$ in relation to the injectate volume. Furthermore, drug which is deposited well away from the dura, such as in the paravertebral space, may not regain access to the dura. It represents an absolute loss of drug dose, which in the model appears as an increase in $V_{ex}$ relative to the injectate volume. A highly lipophilic drug, especially if of high MW, results in an even worse situation. Rapid vascular removal and fat uptake relative to dural transfer may establish concentration gradients away from the dura. In addition, reversible binding to tissues is more pronounced with lipophilic drugs (Hollt and Teschemacher, 1975). Such binding to intervening tissues will slow diffusion, in a fashion analogous to the increase in retention time of lipophilic materials in reverse-phase partition chromatography.

These phenomena, then, are expected to increase substantially $V_{ex}$ relative to the injectate volume. The increase should be relatively greater for the lipophilic high-MW drugs than for their less lipophilic low-MW counterparts.

(ii) Drug will become bound non-specifically to extradural tissues, reducing the free concentration. This will appear again as an increase in $V_{ex}$ in the model. The same mechanism should also increase $k_{abs}$, as discussed previously. There will then be much less overall effect on the efficiency of dural transfer. Non-specific binding of narcotics increases as a function of lipophilicity (Hollt and Teschemacher, 1975).

The effect of the increase in $V_{ex}$ will be to decrease proportionally the efficiency of direct dural transfer.

In the next section, the assumptions of the model are examined as a prelude to the discussion.

## VALIDITY OF THE ASSUMPTIONS OF THE MODEL

Each assumption will be examined in turn:

### (i) *Uniformity and thickness of the dura*

The dura is not uniformly thick. There is a systematic increase in dural thickness in the cephalad direction: thoracic dura is almost twice as thick as lumbar dura (Cheng, 1963). The permeability, *P*, is inversely proportional to dural thickness. Values for lumbar dura will be overestimates for more rostral dura. Within a given region there are localized areas of dural thinning, such as where nerve roots pierce the dura, and these areas will tend to increase the overall dural permeability.

Comparison of drugs using permeabilities determined on single pieces of dura will still remain valid.

### (ii) *Zero intradural drug concentration*

The effect of this assumption may be allowed for easily with a more complicated model. Negligible differences in the extent of dural transfer result, justifying this simplifying assumption.

### (iii) *Extradural dose–volume relationships*

This assumption is quite valid provided that the true nature of the volume term $V_{ex}$ is understood. It is not simply the volume of injectate, but is made to encompass drug which has been effectively lost to dural transfer.

### (iv) *$V_{ex}$ not a function of time*

This is unlikely to be wholly true. The processes of extradural drug distribution are complex and time dependent, and $V_{ex}$ is itself a complicated function of these processes. Such time dependency probably leads to small differences in comparison with those attributable to variations in individual extradural anatomy and in the topology of the extradural dose.

## DISCUSSION OF THE MODEL

This paper is the first of a series concerned with the principles which underlie rational use of spinal narcotics. The model, although simple, allows discussion of the factors responsible for dural transfer. It should be stressed that dural transfer is only one aspect of the series of events culminating in analgesia and other effects. Judgement of clinical efficacy must be based on an integrated overview of the end results. All of the drugs available at present were selected deliberately for parenteral use. The principles established with these narcotics may eventually provide a basis for the development and selection of opiates designed specifically for spinal use. The theory may also indicate the measurements which are worthwhile in order to establish such principles.

For dural transmission this paper suggests:

(1) The volume in which a given dose of drug is administered will, within reason, not be critical.

(2) The less lipophilic small molecular weight drugs such as morphine or pethidine will have the most efficient dural transfer.

(3) Under the best circumstances, the efficiency of dural transfer could be surprisingly high.

(4) It is likely to be the situation-dependent factors which are the cause of variations in dural transfer, leading to variation in clinical effect and even complete failure. Large differences exist between drugs, such as between morphine and buprenorphine (table I). These may subsequently be reduced substantially by differences in c.n.s. penetration and receptor affinity. This will be considered in later papers.

(5) The determination of the absorption rate constant from plasma opiate concentrations after extradural administration could provide a suitable measure of rate processes which compete with dural transmission. Early and frequent samples are required, together with an i.v. dose–decay curve.

Narcotic in sites without access to the dura will contribute to the derived absorption rate constant. The contribution of such narcotic to the plasma concentration will not be reflected in additional c.s.f. opiate concentrations in excess of those produced from blood.

(6) The *in vitro* measurement of dural permeability to narcotics is simple. It would be worthwhile to extend these studies to a wide variety of narcotics, especially as anomalously high values occur (e.g. fentanyl).

Later papers will go on to consider the pharmacokinetic results of the dural transfers estimated here. This will allow comparison with clinical data, and show the typical increase in $V_{\alpha}$ to more than the volume of injectate.

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REFERENCES

Atkinson, R. S., Rushman, G. B., and Lee, J. A. (1977). *A Synopsis of Anaesthesia*, p. 463. Bristol: Wright.

Bartlett, A. J., Lloyd-Jones, J. G., Rance, M. J., Flockhart, I. R., Dockray, G., Bennett, M. R. D., and Moore, R. A. (1980). The radioimmunoassay of buprenorphine. *Eur. J. Clin. Pharmacol.*, **18**, 339.

Beardwell, C. G., Burke, C. W., and Cope, C. L. (1968). Urinary free cortisol measured by competitive protein binding. *J. Endocrinol.*, **42**, 79.

Benson, D. W., Kaufman, J. J., and Koski, W. S. (1976). Theoretic significance of pH dependence of narcotics and narcotic antagonists in clinical anesthesia. *Anesth. Analg. (Cleve.)*, **55**, 253.

Bromage, P. R. (1975). Mechanism of action of epidural analgesia. *Br. J. Anaesth.*, **47**, 209.

—— (1981). The price of intraspinal nacotic analgesia: basic constraints. *Anesth. Analg. (Cleve.)*, **60**, 461.

Bullingham, R. E. S. (1981). Synthetic opiate analgesics. *Br. J. Hosp. Med.*, **25**, 59.

—— McQuay, H. J., and Moore, R. A. (1980). Unexpectedly high plasma fentanyl levels after epidural use. *Lancet*, **1**, 1361.

—— —— —— Bennett, M. R. D. (1980). Buprenorphine kinetics. *Clin. Pharmacol. Ther.*, **28**, 667.

—— —— Porter, E. J. B., Allen, M. C., and Moore, R. A. (1982). Sublingual buprenorphine used postoperatively: ten hour plasma level analysis. *Br. J. Clin. Pharmacol.*, **13**, 665.

Cheng, P. (1963). Epidural space. Anatomical and clinical aspects. *Anesth. Analg. (Cleve.)*, **42**, 398.

Collins, V. J. (1976). *Principles of Anesthesiology*. p. 637. Philadelphia: Lea & Febiger.

Cousins, M. J., Mather, C., Glynn, C., Wilson, P., and Graham, J. (1979). Selective spinal analgesia. *Lancet*, **1**, 1141.

Cowen, M. J., Bullingham, R. E. S., Paterson, G. M. C., McQuay, H. J., Turner, M., Allen, M. C., and Moore, R. A. (1982). A controlled comparison of the effects of extradural diamorphine and bupivacaine on plasma glucose and plasma cortisol in postoperative patients. *Anesth. Analg. (Cleve.)*, **61**, 15.

Curry, A. S., Walker, G. W., and Simpson, G. S. (1966). Gas chromatography of ethanol in blood. *Analyst*, **91**, 1088.

Hollt, V., and Teschemacher, H. J. (1975). Hydrophobic interactions responsible for unspecific binding of morphine-like drugs. *Naunyn-Schmeidebergs Arch. Pharmakol.*, **288**, 163.

Kosterlitz, H. W., Leslie, F. M., and Waterfield, A. A. (1975). Rates of onset and offset of action of narcotic analgesics in isolated preparations. *Eur. J. Pharm.*, **32**, 10.

Kutter, E., Herz, A., and Teschemacher, H. J. (1970). Structure–activity correlations of morphine-like analgesics based on efficiencies following intravenous and intraventricular application. *J. Med. Chem.*, **13**, 801.

Lieb, W. R., and Stein, W. D. (1969). Biological membranes behave as non-porous polymeric sheets with respect to diffusion of non-electrolytes. *Nature (Lond.)*, **244**, 240.

Magora, F., Olshwang, D., Eimerl, D., Shorr, J., Katzenelson, R., Cotev, S., and Davidson, J. T. (1980). Observations on extradural morphine analgesia in various pain conditions. *Br. J. Anaesth.*, 52, 247.

Mays, K. S., Schnapp, M., Lipman, J. J., and North, W. C. (1981). Pain relief after peripheral perineural injection of morphine. *Pain* (Suppl. 1), S120.

Reiz, S., and Westberg, M. (1980). Side-effects of epidural morphine. *Lancet*, 2, 203.

Sastry, B. R. (1979). Presynaptic effects of morphine and methionine-enkephalin in feline spinal cord. *Neuropharmacology*, 18, 367.

Stanski, D. R., Greenblatt, D. J., and Lowenstein, E. (1978). Kinetics of intravenous and intramuscular morphine. *Clin. Pharmacol. Ther.*, 24, 52.

Wang, J. K., Nauss, L. A., and Thomas, J. E. (1979). Pain relief by intrathecally applied morphine in man. *Anesthesiology*, 50, 149.

Weddel, S. J., and Ritter, R. R. (1981). Serum levels following epidural administration of morphine and correlation with post-surgical pain. *Anesthesiology*, 54, 210.

Yaksh, T. L., Jessell, T. M., Gamese, R., Mudge, A.W., and Leeman, S. (1980). Intrathecal morphine inhibits substance P release from mammalian spinal cord *in vivo*. *Nature (Lond.)* 286, 155.

—— Rudy, T. A. (1976). Analgesia mediated by a direct spinal action of narcotics. *Science*, 192, 1357.

## PERMEABILITÄT DER DURA FÜR NARKOSEMITTEL: *IN VITRO* BESTIMMUNG UND ANWENDUNG ZUR EXTRADURALEN VERABREICHUNG

### ZUSAMMENFASSUNG

Es wurden *in vitro* Bestimmungen der Permeabilität der kranialen und lumbalen Dura für verschiedene Substanzen einschließlich einer Anzahl von Narkosemitteln durchgeführt. Auch wird über vorläufige Daten, die an menschlichem, post mortem entnommenem Gewebe erhoben wurden, berichtet. Die Permeabilität hatte eine lineare Beziehung zur umgekehrten Quadratwurzel des Molekulargewichtes. Dies ist die zu erwartende Beziehung für einen Diffusionsprozess, der vom Molekulargewicht abhängig ist. Die unterschiedlichen Masse-Selektivitäts-koeffizienten für die lumbale und kraniale Dura wurden berechnet. Sie waren ähnlich bei 0,8 und 0,9. Dieser Wert war größer als der für Diffusion in einfachen Fößsigkeiten aber viel grüer als der für biologische Lipidmembranen. Dies legt die Vermutung nahe, daß die niedrigen Diffusionsraten mehr eine Eigenart der Dicke der Dura darstellen als eine inhärente Undurchlässigkeit. Es wird ein einfaches Modell für den Transport von Pharmaka durch die Dura beschrieben und auf Narkosemittel angewendet. Der Sinn davon ist, die Faktoren, die eine Rolle beim Transport durch die Dura spielen und, die physiochemischen Eigenarten von Pharmaka in Beziehung zu ihrem Transport durch die Dura zu beschreiben; weltweite Bestimmungen in zukünftigen Studien vorzuschlagen. Das Modell zeigt, daß das Molekulargewicht und die Absorptionsrate wichtige Determinanten der Wirksamkeit des Transportes durch die Dura darstellen. Niedriges Molekulargewicht und langsame Absorption ergeben hohe Transportraten durch die Dura. In der Anwendung auf Narkosemittel könnten diese Faktoren von einer Unterscheidung bis sogar zu einer Größenordnung der Menge führen, die direkt durch die Dura transportiert wird.

## PERMEABILIDAD DURAL A LOS NARCOTICOS: DETERMINACION IN VITRO Y APLICACION A LA ADMINISTRACION EXTRADURAL

### SUMARIO

Se midió *in vitro* la permeabilidad de la duramadre craneal y lumbar a diversas sustancias, incluyendo un cierto número de narcóticos analgésicos. Se presenta también información preliminar sobre materiales humanos post-mortem. La permeabilidad presenta una relación lineal con la inversa de la raiz cuadrada del peso molecular. Esat es la relación prevista para un proceso de difusión que está en función del peso molecular. Se calcularon los coeficientes de selectividad de masa diferencial correspondientes a la duramadre craneal y lumbar; estos fueron similares a 0,8-0,9. Dichos coeficientes fueron superiores a los de difusión en liquidos sencillos pero muy inferiores a los de membranas lipido biológicas. Esto sugiere que las baja tasas de difusión son una propiedad del grosor de la duramadre en vez de una impermeabilidad inherente. Se describe un modelo sencillo para la transferencis de drogas en la duramadre y su aplicación a los narcóticos. Su finalidad fue la de sugerir: los factores existentes en la transferencis de drogas en la duramadre; las propiedades fisico químicas de las drogas relativas a su transferencia por parte de la duramadre; mediciones relevantes a futuros estudios. El modelo indica que el peso molecular de la droga y la tasa de absorción son importantes determinantes de la eficiencia de la transferencia dural. Pesos moleculares bajos y una baja absorción producen altos niveles de transferencia dural. Estos factores podrían producir una diferencia de hasta un orden de magnitud en la cantidad transferida directamente a través de la duramadre, cuando se apliquen a narcóticos.

# PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

## CARDIFF MEETING

JULY 2, 1982

### THE ADDITIVE EFFECT OF NITROUS OXIDE ON RESPIRATORY DEPRESSION IN PATIENTS HAVING FENTANYL OR ALFENTANIL INFUSIONS

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Fentanyl was infused at $3\,\mu g\,kg^{-1}\,h^{-1}$ during and for 1h after surgery in seven patients and alfentanil similarly infused at $20\,\mu g\,kg^{-1}\,h^{-1}$ in eight patients. Anaesthesia was maintained with 67% nitrous oxide in oxygen.

Ventilatory indices were measured before operation, during spontaneous breathing of nitrous oxide and 1 h after the termination of nitrous oxide. At each stage, minute ($\dot{V}_E$) and tidal ($V_T$) ventilation, ventilatory frequency ($f$) and central venous $P_{CO_2}$ were measured, and carbon dioxide responsiveness was estimated from the slope, and intercept ($\dot{V}_E$ at $P_{CO_2} = 7.3$ kPa), of the carbon dioxide rebreathing response curve. Plasma concentrations of fentanyl ($C_{Pf}$) or alfentanil ($C_{Pa}$) in central venous blood were measured by radioimmunoassay. All values are presented as mean ± SEM.

During fentanyl infusion ($C_{Pf} = 3.0 \pm 0.4$ ng ml$^{-1}$) with nitrous oxide $\dot{V}_E$ was $4.6 \pm 0.6$ litre min$^{-1}$ and $f$ was $8.1 \pm 1.2$ b.p.m. compared with $6.1 \pm 0.6$ litre min$^{-1}$ and $12.6 \pm 2$ b.p.m. 1 h after termination of nitrous oxide. During anaesthesia the slopes and intercepts of the carbon dioxide response curves were decreased to $27.9 \pm 8.9\%$ and $17.9 \pm 6\%$ respectively of the values before operation, compared with $39.5 \pm 7.4\%$ and $40 \pm 3.3\%$ 1 h after termination of nitrous oxide ($P < 0.05$ and $P < 0.02$). Mean $P_{aCO_2}$ (central venous $P_{CO_2}$ 0.8 kPa) with nitrous oxide on was $7.6 \pm 0.8$ kPa compared with $6.7 \pm 0.5$ kPa 1h after termination of nitrous oxide (n.s.).

During infusion of alfentanil ($C_{Pa}$ $150 \pm 25$ ng ml$^{-1}$) with nitrous oxide, $\dot{V}_E$ was $4.3 \pm 0.6$ litre min$^{-1}$ and $f$ was $8.3 \pm 1.4$ b.p.m. compared with $5.3 \pm 0.5$ litre min$^{-1}$ and $9.9 \pm 0.8$ b.p.m. 1 h after termination of nitrous oxide. During anaesthesia the slopes and intercepts of the carbon dioxide response curve were decreased to $20.4 \pm 5.7\%$ and $28.6 \pm 6.7\%$ respectively of the values before operation, compared with $52.2 \pm 12.3\%$ and $44.0 \pm 4.7\%$ 1 h after termination of nitrous oxide ($P < 0.005$ and $P < 0.05$). Mean $P_{aCO_2}$ (central venous $P_{CO_2}$ 0.8 kPa) with nitrous oxide on was $8.1 \pm 0.5$ kPa compared with $6.4 \pm 0.3$ kPa 1 h after termination of nitrous oxide ($P < 0.005$).

### CARDIOVASCULAR EFFECTS OF ALFENTANIL ANAESTHESIA

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Alfentanil is a new synthetic extremely short-acting analgesic approximately 73 times as potent as morphine. This study examines the cardiovascular effects of an infusion of alfentanil as a complete anaesthetic for cardiac surgery in 30 patients (23M, 7F). Premedication was with lorazepam 4 mg orally, induction was with alfentanil $125\,\mu g\,kg^{-1}$ and anaesthesia was maintained with alfentanil $0.5\,mg\,kg^{-1}\,h^{-1}$ until the start of cardiopulmonary bypass and alfentanil $0.25\,mg\,kg^{-1}\,h^{-1}$ thereafter until the end of surgery. Pancuronium was used for muscle relaxation and ventilation was with air and oxygen. Every minute from before start of induction until cardiopulmonary bypass the following measurements were made: systolic, diastolic, right atrial, pulmonary arterial, pulmonary capillary wedge pressures, heart rate and cardiac output (measured on a beat-to-beat basis using a Philips pulse contour cardiac output computer precalibrated against thermodilution measurement). Data are presented related to points of maximum stimulation up to 10 min after sternotomy (thereafter surgical manipulation caused wide variations in measured values). Statistical analysis was by analysis of variance and Bonnferroni $t$ test.

There were no statistically significant changes in any of the measured or derived cardiovascular variables at any time during the study period. Twenty-six patients required alfentanil supplementation and two patients required sodium nitroprusside for the control of hypertension before cardiopulmonary bypass. The mean (± SEM) total dose of alfentanil used for the period of surgery (including induction) was $1.5 \pm 0.41\,mg\,kg^{-1}$. One patient became hypotensive on induction of anaesthesia and one patient (excluded from this study) so hypertensive that alfentanil anaesthesia had to be abandoned.

## FENTANYL AND ETOMIDATE PLASMA CONCENTRATIONS IN A TOTAL I.V. ANAESTHETIC TECHNIQUE TO 6H AFTER OPERATION

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Infusions of narcotic analgesics are now widely used in anaesthetic techniques. With fentanyl, Hengstmann, Stoeckel and Schüttler (1980) have suggested an effective steady state plasma concentration of 20 ng ml $^{-1}$, but this was based upon e.e.g. indications for adequacy and in the presence of nitrous oxide. In addition to considerations of the steady state plasma concentrations during anaesthesia, information about the concentrations of the narcotic analgesics after operation is equally important, with possible respiratory depression being an uppermost consideration. This work examines the plasma concentrations of both the hypnotic and analgesic components of a total i.v. anaesthetic technique (etomidate – fentanyl – neuromuscular blocker – IPPV).

Ten patients undergoing elective abdomino-pelvic gynaecological surgery (mean duration 87 min) were anaesthetized using a two-step method (Wagner, 1974) with a combined infusion of etomidate 100 $\mu$g kg $^{-1}$ min $^{-1}$ and fentanyl 1 $\mu$g kg $^{-1}$ min $^{-1}$ for the first 10 min, after which a maintenance infusion of one-tenth followed until termination of surgery. Ventilation was with 30% oxygen in air. A contingency plan to increase the infusion if clinical signs dictated was required for one subject in this study.

Peripheral venous samples were obtained from the opposite arm to that receiving the infusion and were assayed for fentanyl (radioimmunoassay) and etomidate (high performance liquid chromatography). To assess if steady state conditions were achieved, samples were drawn not less than 40 min after commencement of the infusion and again 30 min later, or at the termination of the infusion, whichever occurred first. Postoperative samples were drawn at 0, 15, 30, 45, 60, 120, 240 and 360 min after the infusion ceased.

Preliminary data show steady state conditions were achieved in these patients at a mean plasma concentration of fentanyl 17.65 ± 6.5 ng ml $^{-1}$ and of etomidate 326.63 ± 99.16 ng ml $^{-1}$ ($P < 0.01$ Wilcoxon paired sample test). This concentration of fentanyl is similar to that previously reported effective by Hengstmann, Stoeckel and Schüttler (1980), even though no nitrous oxide has been used in this study. One patient showed a secondary peak of fentanyl concentration after the infusion ceased, and the mean concentration of fentanyl at 6 h after operation was 3.39 ± 1.28 ng ml $^{-1}$.

### REFERENCES

Hengstmann, J. H., Stoeckel, H., and Schüttler, J. (1980). *Br. J. Anaesth.*, **52**, 1021.
Wagner, J. G. (1974). *Clin. Pharmacol. Ther.*, **16**, 691.

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## EFFECT OF ANTI-HYPERTENSIVE THERAPY ON THE PHARMACOKINETICS OF ALTHESIN BY INFUSION TO MAN

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We have previously described the pharmacokinetics of Althesin by infusion to a group of patients with normal hepatic function. Some of these patients were also receiving intercurrent drug therapy. The administration of anti-hypertensive therapy may result in a reduction of cardiac output, and hence a decrease in splanchnic and hepatic blood flow (Branch et al., 1973; Nies, Evans and Shand, 1973). This change in systemic haemodynamics will alter the pharmacokinetics of drugs with a high extraction ratio, such as Althesin.

Eighteen patients, ASA grades I or II, were studied. Nine patients were receiving anti-hypertensive treatment (mean age 60.5 yr; mean weight 64.9 kg), the other nine patients acting as a control group (mean age 47.8 yr; mean weight 69.3 kg). After premedication with papaveretum 0.3 mg kg $^{-1}$ and hyoscine 0.006 mg kg $^{-1}$, anaesthesia was induced with a bolus dose of Althesin (alphaxalone 0.55–0.6 mg kg $^{-1}$) and maintained with 66% nitrous oxide in oxygen supplemented with an infusion of Althesin (alphaxalone 13–30 $\mu$g kg $^{-1}$ min $^{-1}$). The infusion was continued at a constant rate until the end of surgery. Neuromuscular blockade was provided by pancuronium 0.1 mg kg $^{-1}$ and additional analgesia by increments of fentanyl.

Blood samples (arterial) were taken during the infusion of Althesin, and at various times up to 240 min during the decay phase after cessation of the infusion. Plasma alphaxalone concentrations were measured by GLC or GC–MS. Pharmacokinetic variables were derived from the individual post-infusion drug decay curves (table I).

Table I. *Comparison of the pharmacokinetic parameters (mean ± SEM) for nine patients receiving anti-hypertensive treatment, and nine healthy controls. Statistical significance between the two groups using Student's unpaired* t *test.* *P < *0.01;* **P < *0.001*

| | Control group ($n = 9$) | Treated hypertensive group ($n = 9$) |
|---|---|---|
| $\alpha$ (min $^{-1}$) | 0.36 ± 0.08 | 0.30 ± 0.11 |
| $T\frac{1}{2}^{\alpha}$ (min) | 2.84 ± 0.86 | 6.63 ± 2.93 |
| $\beta$ (min $^{-1}$) | 0.0084 ± 0.0011 | 0.0074 ± 0.0014 |
| $T\frac{1}{2}^{\beta}$ (min) | 90.87 ± 7.53 | 112.04 ± 18.52 |
| $V_1$ (litre kg $^{-1}$) | 1.48 ± 0.30 | 0.46 ± 0.10* |
| $V_2$(litre kg $^{-1}$) | 0.69 ± 0.15 | 0.41 ± 0.21 |
| $V^{\beta}$ (litre kg $^{-1}$) | 2.22 ± 0.36 | 1.18 ± 0.36 |
| $Cl_{\mathrm{P}}$ (ml kg $^{-1}$ min $^{-1}$) | 16.89 ± 1.68 | 7.72 ± 1.28** |

The groups showed similar distribution and elimination half-lives, but the patients receiving anti-hypertensive treatment had significantly decreased initial volume of distribution ($V_1$) ($P < 0.01$), and systemic clearance ($Cl_{\mathrm{P}}$) ($P < 0.001$). Within the patients receiving anti-hypertensive treatment, there was no significant difference in $V_1$, $V^{\beta}$, or $Cl_{\mathrm{P}}$ between those treated with $\beta$-receptor antagonists ($n = 5$) and those receiving adrenergic neurone blocking drugs ($n = 4$).

Although the primary effect of these drugs is a reduction in cardiac output, and thus in hepatic blood flow, there is also evidence of an additional effect of propranolol on the intrinsic drug-metabolizing activity of the hepatocyte (Greenblatt, Franke and Huffman, 1978). However, this effect will be of minor importance in the systemic clearance of flow-dependent drugs, such as Althesin. Thus, the administration of i.v. anaesthetic agents with high hepatic clearance rates, may need to be modified in patients receiving drugs which decrease liver blood flow.

ACKNOWLEDGEMENT

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REFERENCES

Branch, R. A., Shand, D. G., Wilkinson, G. R., and Nies, A. S. (1973). *J. Pharmacol. Exp. Ther.*, **184**, 515.

Greenblatt, D. J., Franke, K., and Huffman, D. H. (1978). *Circulation*, **57**, 1161.

Nies, A. S., Evans, G. H., and Shand, D. G. (1973). *Am. Heart J.*, **85**, 97.

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## SOME FACTORS PREDISPOSING TO ALTHESIN HYPERSENSITIVITY

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Despite the apparent unpredictability of hypersensitivity reactions to Althesin, certain factors have been confirmed or suggested. Repeat exposure to the drug is associated with a high frequency of severe reactions, mediated by classical complement pathway activation (Radford, Lockyer and Simpson, 1982). This study has been designed to investigate pregnancy and the dose rate of Althesin administration as possible predisposing factors in patients exposed to the drug for the first time, by the investigation of complement activation in blood samples obtained during routine, apparently uneventful anaesthesia.

Two main groups of patients were studied, 75 pregnant patients undergoing first trimester vaginal termination of pregnancy and 50 non-pregnant premenopausal patients undergoing dilatation and curettage. All patients were ASA I or II and gave preoperative consent to the sampling of blood. Following premedication with papaveretum $0.3\,\mathrm{mg\,kg^{-1}}$ and hyoscine $0.006\,\mathrm{mg\,kg^{-1}}$, pregnant and non-pregnant patients were further randomly allocated to three anaesthetic groups: high-dose Althesin (HDA) ($0.1\,\mathrm{ml\,kg^{-1}}$ induction dose and increments of 1 ml as necessary), low dose Althesin (LDA) ($0.05\,\mathrm{ml\,kg^{-1}}$) and control, receiving thiopentone $4\,\mathrm{mg\,kg^{-1}}$. The induction dose was injected over 15 s and anaesthesia was maintained with 66% nitrous oxide in oxygen, supplemented with 0.75–1.0% trichloroethylene in the LDA and control groups. In the pregnant patients, syntocinon 5 units was given after evacuation of the uterus. In addition, 11 non-pregnant patients receiving minaxolone citrate (induction dose $0.5\,\mathrm{mg\,kg^{-1}}$ and maintenance increments 5 mg) were also studied.

One-millilitre samples of venous blood were taken into EDTA 1 mg for complement studies, at the following times: (1) before premedication; (2) before induction; (3) before surgery; (4) at the end of surgery. After centrifugation and separation, samples were stored at −20 °C. Two-dimensional immunoelectrophoresis using regionally prepared antisera was used to identify conversion of the C3 complement component and in patients showing C3 conversion, C3 and C4 concentrations were measured by rocket immunoelectrophoresis. C3 conversion occurring in sample (3) was considered indicative of an effect of Althesin (or thiopentone): patients in whom conversion occurred in samples (1) or (2) were not included.

No complement conversion was seen in any of the non-pregnant patients, or in the pregnant controls. One patient in the HDA and three in the LDA group showed C3 conversion in sample (3) or sample (4), or both. A further two patients in the HDA group showed signs of mild hypersensitivity, unassociated with complement conversion. These results suggest that pregnancy may increase the frequency of adverse reactions on first exposure to Althesin, although the mechanism for this is not clear. In contrast, there was no direct relationship between the occurrence of C3 conversion in the pregnant patients and the total dose of Althesin administered. No clinical or immunological evidence of adverse reaction was seen in the 11 patients treated with minaxolone.

REFERENCES

Radford, S. G., Lockyer, J. A., and Simpson, P. J. (1982). *Br. J. Anaesth.*, **54** (in press).

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## PILOT STUDY OF A BENZODIAZEPINE ANTAGONIST

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Möhler and Okada (1977) found that the benzodiazepines are bound to discrete receptors on the membranes of the neurones in the c.n.s.

The results of investigations into the displacement of benzodiazepines from their receptors led Hoffman-La Roche to the synthesis of benzodiazepine antagonists. One of the antagonists, an imidazodiazepine, has exhibited low toxicity in animal studies and blocks the action of several benzodiazepines.

We studied these antagonists in a preliminary experimental clinical trial. Six subjects were studied. Each received the antagonist Ro 15 1788 only, the antagonist and flunitrazepam 5 min later, or flunitrazepam then Ro 15 1788 5 min later. E.e.g., e.c.g. cardiovascular indices and breathing were measured continuously for 130 min. The subjects who received the antagonist only remained awake throughout the study.

Five minutes after flunitrazepam, there was a return to the waking state ($D_0$–$E_0$) (see vigilosomnogram, fig. 1) in a few seconds, as a result of giving the antagonist.

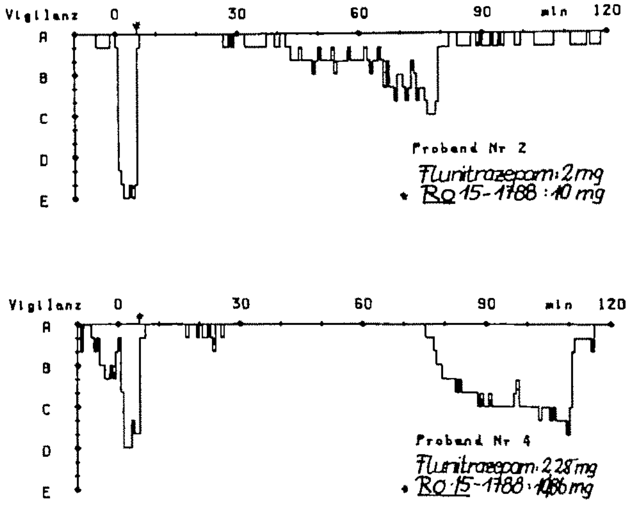

FIG. 1. The vigilosomnograms of two subjects who received flunitrazepam 2 mg/70 kg body weight and, 5 min later, 0.15 mg/kg body weight of the benzodiazepine antagonist. The pre-flunitrazepam state was reached very quickly after the antagonist. Stages of weariness and sleep recurred later.

Following flunitrazepam, obstruction occurred several times so that Esmarch's manipulation had to be applied. Not only vigilance but also respiration became normal within a few seconds after injection of the antagonist.

If the antagonist was given 5 min before flunitrazepam the results were not so impressive. In one subject there were phases of sleep while the other remained awake for 130 min.

Since the subjects were observed in hospital for 12 h we were able to establish that the four who had received flunitrazepam were sound asleep again 4 h after beginning the experiment. It was possible however, to interrupt this sleep by application of arousal stimuli. This observation points to a shorter half-life of the antagonist.

A dose-effect study in 18 subjects will be reported.

The receptor antagonist offers an important new dimension in the use of benzodiazepines.

This study has confirmed the data obtained from our preliminary investigations.

REFERENCE

Möhler, H., and Okada, T. (1977). *Science*, 198, 849.

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# INCREASED GLYCOLYSIS OF MUSCLE IN UNSTRESSED PATIENTS SUSCEPTIBLE TO MALIGNANT HYPERPYREXIA

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Biopsy specimens of the vastus internus muscle were taken from 84 patients undergoing muscle biopsy as a screening procedure to detect susceptibility to malignant hyperpyrexia. Following the results of *in vitro* halothane and caffeine challenges the patients were categorized as either susceptible (MHS) or not susceptible (MHN) to malignant hyperpyrexia. All patients received similar anaesthetics and were from known MH families.

Muscle glycogen was measured in 10 MHS and 10 MHN patients. Following the biopsy the tissue was frozen and kept in liquid nitrogen until analysis (Siu Lo, Russell and Taylor, 1970).

Muscle for lactate and pyruvate from 10 MHS and 10 MHN patients was placed in cold perchloric acid immediately after biopsy. In a separate series, muscle tissue samples from 10 MHS and 14 MHN patients were kept at room temperature for 5 and 60 min after which they were placed in cold perchloric acid. Lactate and pyruvate contents were determined using Boehringer kits 124842 and 124982 respectively.

Muscle for ATP, ADP and AMP from 10 MHS and 20 MHN patients was placed immediately in liquid nitrogen and kept at −80°C until analysed. The determinations were made with Boehringer kits 123897 and 123820 respectively.

The glycogen content of MHS muscle was significantly lower than MHN muscle ($P < 0.001$). The lactate and pyruvate content of MHS muscle was significantly greater than MHN muscle ($P < 0.001$ and $P < 0.001$ respectively), yet the lactate : pyruvate ratio was similar for each group. The lactate content of MHS muscle increased significantly more rapidly than MHN muscle during the first 5 min after biopsy ($P < 0.01$), yet after 60 min the lactate values in both groups, although significantly increased above the

5-min content, were similar ($P > 0.5$). The ATP content of MHS muscle was significantly less than MHN muscle ($P < 0.05$), but the ADP and AMP contents did not differ significantly between the groups. The calculated energy charge did not differ between the two groups (table II).

TABLE II. *All results expressed per 100g wet muscle ± SD*

| | MHS | MHN | P |
|---|---|---|---|
| Glycogen (g) | 0.83 ± 0.14 | 1.22 ± 0.27 | < 0.001 |
| Lactate (mg) | 42.56 ± 9.01 | 20.27 ± 2.91 | < 0.001 |
| Pyruvate (mg) | 1.04 ± 0.20 | 0.58 ± 0.29 | < 0.001 |
| L : P ratio | 41.8 ± 9.6 | 37.1 ± 11.1 | n.s. |
| ATP (mg) | 166.8 ± 68.4 | 256.2 ± 49.6 | < 0.05 |
| ADP (mg) | 49.7 ± 38.2 | 79.5 ± 39.9 | n.s. |
| AMP (mg) | 4.37 ± 1.73 | 7.14 ± 6.13 | n.s. |
| Adenosine (mmol) | 0.451 ± 0.17 | 0.606 ± 0.13 | < 0.05 |
| Energy charge | 0.86 ± 0.08 | 0.87 ± 0.06 | n.s. |

The results show that, even in the unstressed anaesthetized state, muscle taken from patients susceptible to MH shows considerably more glycolytic activity than that from non-susceptible patients. Yet the overall glycolytic potential, as indicated by the highest lactate concentrations reached after 60 supravital minutes, was similar in both groups. These findings provides further evidence of a higher level of sympathetic activity, one of the main determinants of glycolysis in muscle, in patients susceptible to malignant hyperpyrexia.

REFERENCE

Siu Lo, X. X., Russell, J. C., and Taylor, A. W. (1970). *J. Appl. Physiol.*, **28**, 234.

# HORMONE AND METABOLITE CONCENTRATIONS DURING PROGRESSIVELY SEVERE EXERCISE IN MALIGNANT HYPERPYREXIA SUSCEPTIBLE SUBJECTS

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Anecdotal accounts from the United States and Canada have indicated that malignant hyperpyrexia susceptible individuals are at risk of developing hyperpyrexia when under stress or while exercising (Wingard, 1978). No such episodes have been reported in the U.K. Previous work failed to demonstrate any evidence of increased heat production in MH susceptible subjects at rest or with mild exercise. There was, however, indirect evidence of differences in the activity of the sympathetic nervous system between the MHS and a control group (Campbell, and Ellis Evans, 1981). In a further study there was evidence of an abnormality in the heat distribution and dissipation mechanisms in the MHS subjects in that during a period of progressively severe exercise there was a greater increase in central (ear) temperature in the MHS group than in the control subjects and the onset of vasodilatation normally associated with the more severe intensities of exercise was delayed (Campbell and Ellis, 1981). The present communication constitutes the biochemical results associated with this latter study of central and peripheral temperatures during progressively severe exercise.

Five MHS subjects matched for age and sex with five control (mean age 29 yr; four male, one female) were exercised on a cycle ergometer at six to eight incremental work loads, with no rest between each work load from rest up to exhaustion. The period at each work load was 5 min. During the 5th minute blood was taken through an indwelling venous cannula and analysed for lactate, free fatty acids, cortisol, thyroid hormones (TSH, $T_3$, $T_4$) creatine kinase and potassium. Heart rate after 4 min and the values of these hormones and metabolite concentrations at each work load were used to derive interpolated values for each 10-beat increment in heart rate between heart rates of 80 and 180 beat min$^{-1}$. Urinary adrenaline, noradrenaline and dopamine excretion from 30 min before the start of the exercise to 30 min after the finish were measured.

There were no significant differences between the groups with respect to creatine kinase, potassium, $T_3$ or $T_4$. TSH in the controls showed a significant increase between heart rates of 80 and 180 beat min$^{-1}$, but TSH in the MHS group did not. Resting lactate values in the two groups did not differ, but lactate in the MHS subjects was significantly greater than the controls at low exercise intensities at heart rates of 80 and 90 beat min$^{-1}$ ($P < 0.05$) and free fatty acids were greater at heart rates of 160, 170 and 180 beat min$^{-1}$. Plasma cortisol concentrations in both groups increased significantly between heart rates of 80 and 130 beat min$^{-1}$ and continued to increase in the MHS group, but in the controls reverted to values not significantly different from those at 80 beat min$^{-1}$. There were no differences in urinary catecholamine excretion between the groups.

The increase in free fatty acids gives further indirect evidence of an abnormally high level of sympathetic activity in the MHS subjects during a period of progressively severe exercise, although there were no differences in urinary catecholamines. The greater cortisol concentrations imply differences in the "stress response" of the two groups. There is evidence of an abnormality of lactate production probably arising from within the muscle manifest at low (aerobic) intensities of exercise and the existence of which is supported by the findings of the previous presentation. At the higher (anaerobic) exercise levels, this difference is swamped by the increased lactate production from the exercising muscles which appears to be the same in both groups.

Although all subjects were exercised to exhaustion, none showed any undue signs of distress and no cardiac irregularities were noted. The results do not support the notion that with this type and this amount of exercise the MHS subjects were in danger of awake triggering of MH.

REFERENCES

Campbell, I. T., and Ellis, F. R. (1981). *Br. J. Anaesth.*, **53**, 183P.

—— —— Evans, R. T. (1981). *Anesthesiology*, **55**, 46.

Wingard, D. W. (1978). *2nd International Symposium on Malignant Hyperpyrexia*, p. 363. New York: Grune and Stratton.

## SERUM MYOGLOBIN AND CPK RELEASE FOLLOWING SUXAMETHONIUM, STUDIED USING A NEW RADIOIMMUNOASSAY TECHNIQUE

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Suxamethonium administration is associated with an increase in serum potassium concentration and several studies have demonstrated an increase in the concentrations of CPK and urinary myoglobin. Most experimental work on myoglobin has concentrated on urine values, because of the relative insensitivity of earlier tests. This study was designed to look at early serum myoglobin changes following the use of suxamethonium, before the commencement of surgery using a radioimmunoassay technique.

Patients were studied who presented for elective surgery for which intubation with suxamethonium was a reasonable choice of anaesthetic technique. I.m. injections, and patients on therapy with drugs which might have a membrane stabilizing effect were excluded; an oral premedication was prescribed.

On arrival in the anaesthetic room, a cannula was sited in a forearm vein and a blood sample was taken for potassium, CPK and myoglobin measurements. Patients were allocated to pretreatment or no pretreatment groups. Those in the pretreatment group were given a small dose of a non-depolarizing muscle relaxant (e.g. gallamine 20 mg), at least 2 min before induction of anaesthesia. Thiopentone 4 mg kg$^{-1}$ preceded suxamethonium 1 mg kg$^{-1}$ and the trachea was intubated. Thereafter anaesthesia was maintained with narcotics, a non-depolarizing relaxant and IPPV with nitrous oxide in oxygen or spontaneous respiration with volatile anaesthetic and nitrous oxide in oxygen. Further blood samples were drawn at 5, 10 and 20 min after administration of suxamethonium, after which surgery could commence. In some instances when other preoperative preparation took longer than 20 min, a sample was drawn before the incision.

In the initial studies, three of the four patients who had no pretreatment had marked increases in myoglobin concentrations within 10 min, whereas no patient in the pretreatment group had an increased myoglobin concentration. There was no difference between those who received halothane and those who did not. There were no consistent changes in any group in concentrations of CPK and K+ Indeed the K+ changes may merely reflect changes in pH during induction of anaesthesia as no particular effort had been made to control minute ventilation.

Further data will be presented which will allow closer definition of the changes.

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## ACTIONS OF METHOHEXITONE AND TUBOCURARINE AT THE CHICK NEUROMUSCULAR JUNCTION

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The effects of methohexitone and tubocurarine on the depolarizations produced by acetylcholine (Ach) in the isolated chick biventer cervicis (BVC) nerve–muscle preparation were studied using the sucrose-gap apparatus. Methohexitone 5.5–180 $\mu$mol litre$^{-1}$ produced concentration-dependent hyperpolarizations in the chick BVC muscle. Mean ED$_{50}$ for the hyperpolarizations was 42.0 $\pm$ 0.03 $\mu$mol litre$^{-1}$, $n = 6$. Acetylcholine 5.5 $\mu$mol litre$^{-1}$ to 11 mmol litre$^{-1}$ produced depolarizations which were concentration-dependent. These responses were reduced greatly by methohexitone 88 $\mu$mol litre$^{-1}$ and by tubocurarine 12.7 $\mu$mol litre$^{-1}$ respectively. High concentrations of ACh always produced small depolarizations accompanied by marked afterhyperpolarizations. Mean ED$_{50}$ for ACh depolarizations in the control Krebs solution and in methohexitone were 0.89 $\pm$ 0.59 mmol litre$^{-1}$ and 24.0 $\pm$ 0.09 mmol litre$^{-1}$ ($n = 6$), respectively. A mean ED$_{50}$ ratio of 26.9 $\pm$ 1.02 : 1.0 (test/control) was obtained. A mean maximum depolarization of 4.9 $\pm$ 1.8 mV ($n = 6$) was obtained with ACh 5.5 mmol litre$^{-1}$ in the control Krebs solution. Mean ED$_{50}$ for ACh depolarizations in the control Krebs solution and in tubocurarine were 0.77 $\pm$ 0.56 mmol litre$^{-1}$ and 3.2 $\pm$ 0.06 mmol litre$^{-1}$ ($n = 6$) respectively. A mean ED$_{50}$ ratio of 4.2 $\pm$ 0.34 : 1.0 (test/control) was obtained. Methohexitone 88 $\mu$mol litre$^{-1}$ greatly reduced the depolarizations produced by ACh and shifted the concentration–response curve to the right in a non-competitive manner. Tubocurarine 12.7 $\mu$mol litre$^{-1}$ also reduced these depolarizations, but to a lesser extent, and shifted the concentration–response curve to the right in a competitive manner. These actions were reversible upon washing out the methohexitone and tubocurarine, but recovery took more than 1 h after methohexitone and less than 30 min after tubocurarine. Thesleff (1956), working on frog sartorius muscle, found that sodium pentobarbitone reduced the postsynaptic responses to electrophoretically applied ACh or carbachol. Gingsborg and Warriner (1960), working on the chick BVC muscle, found that tubocurarine 14.0 $\mu$mol litre$^{-1}$ blocked the twitch contractions evoked by supramaximal nerve stimulation at 0.2 Hz, and reduced the contracture responses produced by ACh 13.0 $\mu$mol litre$^{-1}$. Neostigmine 3.3 $\mu$mol litre$^{-1}$ reversed the neuromuscular blockade produced by tubocurarine. Adams (1976), working on frog sartorius muscle, showed that barbiturates block open, but not closed, end-plate channels and reduce the time course of the end-plate current produced by ACh or carbachol. The depressant actions of methohexitone on ACh-induced depolarizations, in these experiments, may be explained if methohexitone acts by blocking (non-competitively) the ACh receptors or by blocking the end-plate channels activated and opened by ACh, or both, in the manner suggested by Adams (1976).

### REFERENCES

Adams, P. R. (1976). *J. Physiol.* (*Lond.*), **260**, 531.

Ginsborg, B. L., and Warriner, J. (1960). *Br. J. Pharmacol.*, **15**, 410.

Thesleff, S. (1956). *Acta Physiol. Scand.*, **37**, 335.

## PLASMA CATECHOLAMINE RESPONSES TO ENDOTRACHEAL INTUBATION

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The measurement of the stress response to anaesthesia and surgery has been the subject of many investigations, centred upon the preoperative and postoperative measurement of cortisol, growth hormone and, more recently, catecholamine concentrations in plasma. Endotracheal intubation produces a considerable stimulus to the patient under anaesthesia and is associated with significant cardiovascular disturbance, particularly in hypertensive patients.

Russell and others (1981) found that plasma concentrations of noradrenaline were increased immediately following endotracheal intubation and this correlated with an increase in mean arterial pressure. Although plasma adrenaline concentration increased, the change in adrenaline was not statistically significant. However, in more extensive studies of catecholamine responses to surgery, Stanley and others (1980) and Hoar and colleagues (1981) were unable to demonstrate any changes following endotracheal intubation.

Recently we have presented to the Society a method of measurement of plasma catecholamines using HPLC, which is accurate and relatively economical. Using this technique, we have measured plasma catecholamines in response to endotracheal intubation in an attempt to answer three questions. First, can we confirm an increase in plasma noradrenaline in response to endotracheal intubation and in addition is this accompanied by a significant change in adrenaline? Second, are there any differences in this response when intubation is carried out following suxamethonium in comparison with pancuronium? Third, are there any appreciable differences in results when blood samples are taken from different sampling sites?

Following a standard anaesthetic premedication (diazepam 10 mg and droperidol 2.5 mg) and induction (thiopentone 3–4 mg kg$^{-1}$), patients were given either suxamethonium 1 mg kg$^{-1}$ or pancuronium 0.1 mg kg$^{-1}$ to facilitate endotracheal intubation. Blood samples were withdrawn simultaneously from a peripheral venous, a central venous and a radial arterial cannula.

To date, measurements have been obtained in 14 patients given either suxamethonium or pancuronium. Overall mean plasma concentrations of noradrenaline were $1.74 \pm 0.72$ pmol ml$^{-1}$ (mean ± SD) before operation, $1.63 \pm 0.70$ pmol ml$^{-1}$ immediately after induction, $3.95 \pm 2.09$ pmol ml$^{-1}$ immediately after endotracheal intubation and $2.65 \pm 1.28$ pmol ml$^{-1}$ 5 min after intubation (in radial arterial samples). The corresponding values for adrenaline were $0.64 \pm 0.52$; $0.55 \pm 0.43$, $1.20 \pm 0.74$ and $0.56 \pm 0.29$ pmol ml$^{-1}$ respectively.

These increases in catecholamine concentrations corresponded to changes in mean arterial pressure. The changes in central venous blood samples were more marked than corresponding changes in radial arterial or peripheral venous samples.

### REFERENCES

Hoar, P. F., Nelson, N. T., Mangano, D. T., Bainton, C. R., and Hickey, R. F. (1981). *Anesth. Analg. (Cleve.)*, **60**, 406.

Russell, W. J., Morris, R. G., Frewin, D. B., and Drew' S. E. (1981). *Br. J. Anaesth.*, **53**, 837.

Stanley, T. H., Berman, L., Green, O., and Robertson, D. (1980). *Anesthesiology*, **53**, 250.

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## BRONCHIOLECTASIS AS A RESULT OF ARTIFICIAL VENTILATION WITH POSITIVE END-EXPIRATORY PRESSURE

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Pulmonary barotrauma associated with artificial ventilation is recognized clinically as pneumothorax, pneumomediastinum or subcutaneous emphysema, or both (Kumar et al., 1973). We have, however, observed in patients dying after artificial ventilation a hitherto undescribed histological appearance of gross dilatation of the terminal and respiratory bronchioles, with collapse of surrounding alveoli. The lungs were fixed in inflation using the method of Wright and others (1974). The histological appearances suggest that, in severe cases, the dilated bronchioles would receive the greater part of the tidal exchange.

In a retrospective study of 11 patients who had died after a period of artificial ventilation, the degree of bronchiolectasis was independently scored on a scale 0–8 by two histopathologists who were unaware of the patient's ventilatory history. The bronchiolectasis score was then related to variables characterizing the circumstances of the artificial ventilation using stepwise multiple regression analysis and Kendall's rank correlation test.

The strongest correlation was with the maximal value of positive end-expiratory pressure (PEEP) ($P < 0.001$). When this factor was excluded, there remained a strong correlation with the duration of PEEP leading to the following multiple regression equation: degree of bronchiolectasis = 0.395 + 2.88 PEEP (kPa) + 0.166 duration of PEEP (days). The multiple correlation coefficient is 0.958 and the regression equation accounts for 91.8% of the variability in the bronchiolectasis score. The four patients who did not receive PEEP showed no sign of bronchiolectasis. Kendall's rank correlation test selected the same two variables, but in the reverse order of significance (duration of PEEP, $r = 0.894$; level of PEEP, $r = 0.74$).

Physiological deadspace was not measured in the patients, but the product of pulmonary minute volume and arterial $P\text{CO}_2$ is an inverse function of $[1 - (V\text{D}/V\text{T})]$ if carbon dioxide output is considered to remain constant. There was in fact a strong correlation between the observed degree of bronchiolectasis and the product of minute volume and arterial $P\text{CO}_2$ with a correction to normalize carbon dioxide output to that of a young male adult at 37 °C ($r = 0.90$, $P < 0.001$). Values suggested $V\text{D}/V\text{T}$ ratios of the order of 90% in the most severe cases. This is sufficiently large to impose major difficulties in securing gaseous homeostasis.

A prospective study with all variables controlled is not possible under these conditions. Nevertheless our results suggest that the level and duration of PEEP may be the major factors in the development of bronchiolectasis and that this is associated with an increased $V_D/V_T$ ratio. It is not yet known whether the changes of bronchiolectasis resolve in surviving patients, but the position is complicated by the existence of other major pulmonary pathology which constituted the requirement for ventilatory support.

REFERENCES

Kumar, A., Pontoppidan, H., Falke, K. J., Wilson, R. S., and Laver, M. B. (1973). *Crit. Care Med.*, **1**, 181.

Wright, B. M., Slavin, G., Kreel, L., Callan, K., and Sandin, B. (1974). *Thorax*, **29**, 189.

## CARDIOVASCULAR EFFECT OF A NITROPRUSSIDE-TRIMETAPHAN MIXTURE DURING HALOTHANE ANAESTHESIA

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The haemodynamic effects of induced hypotension with a mixture of sodium nitroprusside and trimetaphan (MacRae, Wildsmith and Dale, 1981) have been studied during halothane anaesthesia with a 5° head-up tilt in 12 patients. Six breathed spontaneously and six were artificially ventilated.

After induction of anaesthesia, but before surgery, control readings were made of cardiac output (dye dilution method), heart rate and mean arterial and central venous pressures. Hypotension (systolic arterial pressure 60 mm Hg) was induced and the measurements repeated. Further measurements were made after the start and at the end of surgery, then after levelling of the operating table, and finally after discontinuation of the hypotensive agents. Stroke volume and peripheral resistance were derived from the primary measurements.

In both groups there was a rapid controllable decrease in arterial pressure with a decrease in peripheral resistance. Stroke volume decreased, but the increases in heart rate were not statistically significant. Cardiac output was little changed in patients who breathed spontaneously, but decreased in all those artificially ventilated. C.v.p. decreased in both groups, but to a greater degree during spontaneous than during artificial ventilation.

The start of surgery was associated with a further increase in heart rate and the rate of drug infusion had to be increased in nearly all patients to maintain hypotension. Cardiac output had increased by the end of surgery in both groups, although this was not statistically significant in the artificially ventilated group. Levelling the operating table produced further increases in cardiac output.

On discontinuation of the hypotensive drugs arterial pressure returned rapidly to control values.

REFERENCE

MacRae, W. R., Wildsmith, J. A. W., and Dale, B. A. B. (1981). *Anaesthesia*, **36**, 312.

## MIDAZOLAM AS A SEDATIVE IN ENDOSCOPY

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As with other benzodiazepines, midazolam is too variable in action to be used as a routine induction agent (Gamble et al., 1981). Nevertheless, it is worthy of study in other circumstances in which one uses diazepam. We report here its use as an adjuvant to local anaesthesia in 234 patients of both sexes having oesophagogastroduodenoscopy.

Patients were generally in the elderly age group (mean 51 ± 2 yr). Initially midazolam was given by an anaesthetist, but in the last 100 patients it was administered by the endoscopist.

Arterial pressure and heart rate were recorded frequently in all patients, as was clinical evidence of respiratory depression. No significant changes were found and subsequent data relate to operating conditions which were graded as good, fair or poor by the anaesthetist and endoscopist.

In some patients, recovery was studied using the pegboard test (Carson, Graham and Dundee, 1975).

TABLE III. *Mean dose (± SEM) of benzodiazepine used, operating conditions as agreed by operator and anaesthetist and average time (± SEM) to return to normal pegboard test*

| Technique | *n* | Dose (mg) | Conditions (%) Good | Fair | Recovery *n* | (min) |
|---|---|---|---|---|---|---|
| Midazolam | | | | | | |
| Fixed dose | | | | | | |
| 0.07 mg kg$^{-1}$ | 40 | | 68 | 10 | | |
| As required | | | | | | |
| given by anaesthetist | 54 | 7.1 ± 0.5 | 54 | 28 | 21 | 82 ± 9.7 |
| given by endoscopist | 100 | 4.9 ± 0.2 | 59 | 32 | | |
| with pentazocine | 40 | 6.0 ± 0.5 | 78 | 10 | 9 | 78 ± 9.0 |
| Diazepam | | | | | | |
| As required | | | | | | |
| given by endoscopist | 68 | 8.5 ± 0.5 | 63 | 24 | 13 | 70 ± 16.5 |

Initially a fixed dose of 0.07 mg kg$^{-1}$ (mean 4.4 mg) was given (table III). Operating conditions varied with age; in only eight of 20 aged 20–60 yr were the conditions classed as good, as compared with 19 of 20 in the 61+ age group. This was paralleled by the frequency of amnesia.

With midazolam given slowly as required until the desirable effect was produced the average dose was slightly greater (0.09 mg kg$^{-1}$, 5.6 mg) and the frequency of acceptable (good and fair) conditions significantly increased ($\chi^2 = 4.02$; $P < 0.05$). It can be seen that the anaesthetist used a significantly greater average dose ($t = 4.9$; $P < 0.0005$) than the endoscopist. Dosage was reduced as the technique evolved, averaging 0.105 mg kg$^{-1}$ (6.7 mg) in the first 10 and 0.09 mg kg$^{-1}$ (5.8 mg) in the last 10 administrations by the anaesthetist.

The addition of pentazocine (mean dose 25 mg) improved slightly operating conditions.

Our overall frequency was 85% acceptable operating conditions, which compares favourably with the findings with diazepam, as does the recovery time. However our ratio of potency of midazolam to diazepam was 1.7 : 1, rather than the 2.0 generally stated.

REFERENCES

Carson, I. W., Graham, J., and Dundee, J. W. (1975). *Br. J. Anaesth.*, **47**, 358.

Gamble, J. A. S., Kawar, P., Dundee, J. W., Moore, J., and Briggs, L. P. (1981). *Anaesthesia*, **36**, 868.

# POSTER DEMONSTRATIONS

## MIDAZOLAM AS A SEDATIVE IN DENTISTRY

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Diazepam is widely used as a sedative–hypnotic for dental procedures carried out under local anaesthesia. This is a report of findings in 62 patients who were given the water-soluble benzodiazepine in place of diazepam, compared with 17 patients given diazepam.

Patients had been referred to hospital because of fear, or unwillingness to have dental treatment under local anesthesia alone. Procedures included extractions, apicectomy and conservative dentistry. The majority of patients were fit young women (table IV). No premedication was given.

The planned doses were midazolam 0.1 mg kg$^{-1}$ and diazepam 0.2 mg kg$^{-1}$, the former being comparable to that used by Dixon and Thornton (1973). Lignocaine 2% with adrenaline was injected 2 min after the benzodiazepine and the completeness of the local block tested before surgery began. Because of the intensity of the sedation this was difficult following midazolam and after seven patients half the dose was given followed by the remainder when it was established that the block was adequate. Before the local injection patients were asked if they felt more relaxed or remained anxious.

Patients were all in the sitting position and cardiovascular effects were recorded routinely. Attention was paid to airway obstruction and clinical evidence of respiratory depression. Operating conditions were graded by the dentist as excellent, good, fair or poor. Where possible, time to recovery was assessed by the pegboard test (Carson, Graham and Dundee, 1975). Before leaving hospital patients were questioned for memory of the local injection and intra-operative events and asked if they would have the same drug again.

TABLE IV. *Details of patients and summary of findings*

| | Midazolam ($n = 62$) | Diazepam ($n = 17$) |
|---|---|---|
| Patients | | |
| (average ± SEM) | | |
| Age (yr) | 27 ± 3.2 | 30 ± 1.7 |
| Weight (kg) | 57 ± 1.1 | 58 ± 2.5 |
| F/M | 61/1 | 15/2 |
| Pain on injection | 1 | 14 |
| Operating conditions | | |
| Excellent | 44 | 12 |
| Good | 11 | 3 |
| Fair | 3 | 2 |
| Poor | 4 | 0 |
| Amnesia—complete | 52 | 9 |
| Would have same drug again | 62 | 15 |
| Recovery time (min) as assessed by pegboard | 63.5 ± 4.1<br>(42) | 63.2 ± 6.1<br>(8) |

All patients felt more relaxed after the benzodiazepines and operating conditions were generally acceptable. In one of the failures with midazolam local anaesthesia may have been inadequate, while three reacted to pressure or drilling. Complete amnesia occurred more frequently with midazolam than diazepam ($\chi^2 = 7.25$; $P < 0.005$). Recovery was similar with both drugs.

REFERENCES

Carson, I. W., Graham, J., and Dundee, J. W. (1975). *Br. J. Anaesth.*, **47**, 358.

Dixon, R. S., and Thornton, J. A. (1973). *Br. J. Anaesth.*, **45**, 207.

## DOSE-RESPONSE EFFECT OF ALTHESIN INFUSION ON THE E.E.G.: INFLUENCE OF AGE AND OBESITY

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Assessment and control of depth of anaesthesia are major problems of i.v. infusion anaesthesia, and factors influencing variations between patients have not been investigated.

We have studied the e.e.g. (electroencephalogram) in 12 patients undergoing transphenoidal hypophysectomy. Different infusion rates of Althesin were used to supplement nitrous oxide–relaxant anaesthesia and the e.e.g. depth of anaesthesia (Prior, Maynard and Brierly, 1978) was determined every 5 min.

For any individual patient the relationship between infusion rate (ml $h^{-1}$) and e.e.g. level is reasonably linear. However, the variability about the straight line and the slope of the line differ considerably from patient to patient.

A straight line was fitted for each patient by least squares and the Althesin infusion rate corresponding to e.e.g. level 3 was noted. The mean infusion rate for e.e.g. level 3 is 20 ml $h^{-1}$ and the infusion rate which will produce this level in 95% of patients (95% prediction interval, denoted by $I_{95\%}$) is 36 ml $h^{-1}$. On the other hand, this infusion rate would produce an e.e.g. level of more than 5 in at least 50% of patients.

There was some evidence that age and obesity correlated with a lower infusion rate required to produce e.e.g. level 3 ($r = -0.45$, $P < 0.1$, $r = -0.51$, $P < 0.1$ respectively). However, other factors must be involved in the variation between patients.

REFERENCE

Prior, P. F., Maynard, D. E., and Brierley, J. B. (1978). *Br. J. Anaesth.*, **50**, 993.

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## ASSESSMENT OF RECOVERY FROM DAY-CASE ANAESTHESIA SUPPLEMENTED WITH ALFENTANIL

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Alfentanil is a narcotic analgesic with a very rapid onset of action and very short duration of action (Niemegeers and Janssen, 1981). This study investigated recovery after anaesthesia consisting of increments of an i.v. hypnotic with alfentanil to induce and maintain anaesthesia supplemented by 66% nitrous oxide in oxygen.

Forty patients (18–51 yr) undergoing minor gynaecological surgery were studied. Informed consent was obtained from all patients. They were allocated randomly to receive alfentanil 8 μg $kg^{-1}$ followed by either Althesin 50 μl $kg^{-1}$ (group A) or methohexitone 1.5 mg $kg^{-1}$ (group B) i.v. for induction of anaesthesia. Increments of Althesin 0.5 ml or methohexitone 10 mg were given on movement by the patient. Recovery was assessed by an independent anaesthetist unaware of the anaesthetic given, using the methods of Cooper, Craig and Sear (1981). This involved the use of a "Kiddicraft" post-box and deletion of the letter *p* from a page of letters. Times after discontinuing nitrous oxide until the patient opened her eyes and until she was able to give her correct date of birth, were noted. At 5-min intervals the patient was asked to attempt the post-box test. When the pre-operative value was attained she was then again asked to delete *p*. Statistical analysis of the results was performed on logarithmically transformed values because of skewness of the data.

There was no difference in the age, weight, height or duration of anaesthesia between each group, nor any difference between the two groups in the times to completing the indices of recovery (table V). Deletion of *p*– test was analysed with regard to lines completed and errors made. After operation no more errors were made but fewer lines were completed in both groups ($P < 0.05$), and there was no difference between the groups.

Table V. *Three indices of recovery in the two groups of 20 patients (mean and 95% confidence limits)*

| | Althesin and alfentanil (group A) | Methohexitone and alfentanil (group B) |
|---|---|---|
| Eyes open (min.) | 2.6 (0.8– 8.1) | 2.1 (0.4–12.3) |
| Date of birth (min.) | 4.1 (1.7– 9.8) | 3.3 (1.4– 7.6) |
| Post-box (min.) | 25.0 (7.9–79) | 25.7 (8 –83) |

Comparison with the previous study (Cooper, Craig and Sear, 1981) shows that those who received alfentanil completed the post-box test more quickly than those who received either no analgesic or fentanyl ($P < 0.05$).

REFERENCES

Cooper, G. M., Craig, J. F., and Sear, J. W. (1981). *Br. J. Anaesth*, **53**, 1094.

Niemegeers, C. J. E., and Janssen, P. A. J. (1981). *Drug Devel. Res.*, **1**, 83.

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## ICI 35868 PHARMACOKINETICS IN HUMANS: SINGLE DOSE STUDIES

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ICI 35868 2 mg $kg^{-1}$ was used to induce anaesthesia in 22 fit unpremedicated women, scheduled for minor gynaecological procedures. Three different injection speeds were examined: over 3–5,. 20 or 40–50 s. Each subject was allowed to recover, as assessed by time to eye opening and giving correct date of birth, before anaesthesia was re-introduced with thiopentone and maintained by nitrous oxide, alone or in combination with trichloroethylene or methoxyflurane. In two additional patients, given ICI 35868 4 mg kg$^{-1}$, the gynaecological procedure was carried out without additional agents.

Concentrations of drug were measured up to 4h after administration. Pharmacokinetic analysis was carried out on the data, after allowing a finite mixing time and correcting for the duration of the injection. This showed that the speed of injection and the presence of additional agents had little effect on the concentration profile. Thus the pharmacokinetics of ICI 35868 in man are characterized by a relatively large initial volume of distribution (37 litre) and an extremely rapid distribution phase (half-life 2.5 min) into a large apparent volume of distribution (271 litre). However, clearance from the body is rapid with a terminal elimination half-life of 55 min and a total body clearance of 3454 ml min$^{-1}$.

After a 2-mg kg$^{-1}$ dose the mean recovery times were 4.4 min to eyes open and 5.2 min to giving date of birth. These were unaffected by the speed of injection. Equally, the mean concentrations at recovery, 1.05 $\mu$g ml$^{-1}$ at eyes open and 0.9 $\mu$g ml$^{-1}$ at giving date of birth were also unaffected by speed of injection.

These observations on the pharmacokinetics of ICI 35868 are in total accord with previous clinical observations and explain the rapid recovery which is characteristic of this agent.

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## CHANGES IN ($P\mathrm{AO}_2 - P\mathrm{aO}_2$) ARE UNRELATED TO CHANGES IN LUNG VOLUME DURING ANAESTHESIA

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The alveolar arterial oxygen gradient ($P\mathrm{AO}_2 - P\mathrm{aO}_2$) increases with the induction of anaesthesia, leading to reduced arterial oxygen tension. Simultaneously, lung volume decreases, and this decrease has been thought to be the cause of the worsening gas exchange. However, increasing lung volume with PEEP only slightly improves gas exchange (Wyche, Teichner and Kallos, 1973) even when the PEEP was adjusted so that FRC was just greater than CC (Tien and Bergman, 1980).

We have investigated further the link between lung volume and oxygenation. We increased lung volume in anaesthetized patients by tilting them head-up, and measured their ($P\mathrm{AO}_2 - P\mathrm{aO}_2$) head-up and supine.

Expiratory reserve volume (ERV) and ($P\mathrm{AO}_2 - P\mathrm{aO}_2$) were measured before operation in 18 patients. ERV was measured by simple spirometry, ($P\mathrm{AO}_2 - P\mathrm{aO}_2$) using the same inspired oxygen concentration ($F\mathrm{IO}_2$), ±1%, as during anaesthesia. After lorazepam premedication anaesthesia was induced. The first 12 patients received thiopentone and pancuronium and were ventilated with 30–40% oxygen in nitrous oxide. Because of a possible effect of nitrous oxide uptake on alveolar $P\mathrm{O}_2$, a further six patients were anaesthetized with an infusion of etomidate, given pancuronium, and ventilated with 30–40% oxygen in nitrogen. ERV, $F\mathrm{IO}_2$, $P\mathrm{aO}_2$ and $P\mathrm{aCO}_2$ were measured in all patients, both supine and approximately 30° head-up. The order of positions was varied, and eight patients were put head-up first. In 11 patients cardiac output ($\dot{Q}$) during anaesthesia was assessed using transaortic velography (Sequira et al., 1976). ERV was defined, in anaesthetized patients, as the volume of gas withdrawn from the lung by application of a pressure of $-30$ cm $H_2O$ to the airway. The volume was measured with a gas syringe or a pneumotachograph. $P\mathrm{AO}_2$ was calculated as $P\mathrm{IO}_2 - P\mathrm{aCO}_2/R + F\mathrm{IO}_2$, $P\mathrm{aCO}_2$, $(1-R)/R$ where $R = 0.8$ (assumed).

Statistics were analysed by two-way analysis of variance and multiple linear regression analysis.

ERV was significantly larger when 30° head-up than when supine awake or anaesthetized. ($P\mathrm{AO}_2 - P\mathrm{aO}_2$) was not consistently different when head-up, and the change in ($P\mathrm{AO}_2 - P\mathrm{aO}_2$) with position did not correlate with the change in ERV or $\dot{Q}$. There was a correlation between ($P\mathrm{AO}_2 - P\mathrm{aO}_2$) and order of positions, ($P\mathrm{AO}_2 - P\mathrm{aO}_2$) being greater in the second position irrespective of which it was. However, this effect disappeared with the application of multiple linear regression analysis, which takes into account interdependence of variables.

Our failure to demonstrate consistent changes in ($P\mathrm{AO}_2 - P\mathrm{aO}_2$) in response to lung volume changes during anaesthesia suggests that the changes in the two variables, which are associated with onset of anaesthesia, are coincidental. These changes are probably responses to some other phenomena, still unidentified, associated with anaesthesia.

### REFERENCES

Sequira, R. F., Light, L. H., Cross, G., and Raftery, E. B. (1976). *Br. Heart J.*, **38**, 443.

Tien, Y. K., and Bergman, N. A. (1980). *Anesthesiology*, **53**, S413.

Wyche, M. Q., Teichner, L., and Kallos, T. (1973). *Anesthesiology*, **38**, 69.

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## IS CHRONIC EXPOSURE TO ENFLURANE TERATOGENIC OR TOXIC AT 200 p.p.m.? A STUDY IN RATS

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In an earlier study (Halsey et al., 1981) we exposed male and female rats to enflurane 20 p.p.m. before mating and during pregnancy in accordance with Committee on Safety of Medicines requirements. We have now carried out a more stringent test following exposure of male or female rats to enflurane 200 p.p.m. In addition, the validity of our animal model has been tested for the first time with a known teratogen, Vitamin A palmitate.

Adult Sprague–Dawley rats were exposed in two chambers with controlled environments, one of which contained enflurane 200 p.p.m. for 8 h on 5 consecutive days per week. There were three types of treatment: (1) Male rats were exposed to enflurane for 63 days and mated with untreated rats ($n = 30$). The males continued to be exposed for a further 37 days. (2) Female rats ($n = 20$) were exposed to enflurane for 28 days, mated with untreated rats ($n = 20$) in an enflurane-free environment, then treatment was continued throughout pregnancy. (3) Pregnant rats ($n = 20$) were orally dosed with Vitamin A palmitate 30 000 i.u. on days 5–13 of pregnancy. Each group had its own control ($n = 20$) housed in a separate chamber.

Male rats were killed after 100 days exposure and samples of liver, kidney, lung, spleen, testes and heart were prepared for histological examination. Pregnant rats were killed on day 21 of pregnancy. Maternal liver and kidney were weighed and fixed. Litter and fetal measurements made were: litter size, resorptions, fetal weight, placental weight, crown–rump length and sex. Fetuses were fixed in 95% alcohol, stained with Alzarin Red-S and assessed for osseous development. Data were subjected to Student's *t* test or a comparison of proportions.

Chronic exposure to enflurane 200 p.p.m. had no significant effect on adult body weights. Histologically there was no evidence of organ toxicity in males or females; nor were pregnancy, litter size, fetal wastage or fetal size significantly different in the enflurane-exposed groups. The overall frequency of fetal skeletal abnormalities was 10% (normal for this strain)—mainly supplementary ribs and reduced phalangeal ossification—but no relationship between enflurane treatment and abnormality was demonstrated.

In contrast, treatment with Vitamin A palmitate resulted in gross abnormalities, 21% of fetuses being acephalic ($P < 0.001$) and 3.6% of fetuses having cleft palate ($P < 0.05$). Other abnormalities occurred in 85% of fetuses in this group, compared with 20% of the control group.

In conclusion, we could not demonstrate fetal or histological toxicity in these experiments with enflurane 200 p.p.m. over periods of 1–4 months. We have, however, shown that the rat strain chosen is susceptible to a known teratogen.

REFERENCE

Halsey, M. J., Green, C. J., Monk, S. J., Doré, C., Knight, J. F., and Luff, N. P. (1981). *Br. J. Anaesth.*, **53**, 203.

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# ENFLURANE, CRITICAL CORONARY STENOSIS, AND LEFT VENTRICULAR DIASTOLIC RELAXATION

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Extensive investigation of the actions of general anaesthetic agents and techniques on myocardial performance continues, but because of the emphasis on systolic contractile function, coupled with the difficulty experienced in making relevant measurements, little has been published concerning the modification of diastolic events by anaesthesia.

It is our hypothesis that interference with the normal processes of ventricular diastole—namely isovolumic relaxation, rapid ventricular filling, "diastasis" and atrial contraction—might contribute to the disproportionate increases in atrial pressures observed during administration of inhalation anaesthetics. A proper understanding of such acute changes, particularly when they are superimposed upon pre-existing cardiac disease, would allow insight into the physiological basis for the serious complications suffered by cardiac patients during and after surgery.

To test this theory we are currently making a systematic review of data from our earlier studies with enflurane in a dog model, before and after instituting critical stenosis of the left anterior descending (LAD) coronary artery. The preparation of the model has been described previously (Cutfield et al., 1980). This report describes the results of measurements of one index of early diastolic relaxation: the time constant of left ventricular isovolumic pressure decrease, $\tau$. This measurement was originally described by Weiss, Frederiksen and Weisfeldt (1976) and has subsequently been shown to be a sensitive indicator of myocardial relaxation, while remaining independent of ventricular preload, afterload or heart rate.

High fidelity recordings of left ventricular pressure (LVP) were analysed at 4-ms intervals, from the time of maximum negative LV $dP/dt$ to the time (before mitral valve opening) when LVP reached a value 10 mm Hg greater than left atrial pressure. During this period, LVP decline follows an exponential course, such that plotting the logarithm of instantaneous LVP against time yields a straight line. The negative reciprocal of the slope of this linear relationship is the time constant of pressure decrease.

TABLE VI. *Comparison of the effects of enflurane, before and after establishing critical LAD coronary stenosis, on the time constant of left ventricular isovolumic pressure decline and other variables. Control column gives mean percent change from 0.5 MAC to 1.5 MAC enflurane before coronary stenosis (all significant to* $P < 0.01$*). Critical stenosis column gives mean percent change over same dose range with LAD stenosis. Statistical comparison between the two columns:* *$P < 0.05$, $n = 6$*; values are mean (1 SEM)*

| | Control | Critical LAD stenosis |
|---|---|---|
| Time constant, $\tau$ | +38% | +75% |
| | (9) | (9)* |
| LV end-diastolic pressure | +31% | +89% |
| | (14) | (40)* |
| LV $dP/dt$ max | −50% | −58% |
| | (4) | (4)* |
| Stroke volume | −24% | −49% |
| | (6) | (7)* |

The results of this study are summarized in table VI. Using linear regression analysis to derive $\tau$, the minimum value of the correlation coefficient was 0.996, which confirms the mono-exponential nature of isovolumic LVP decline in this model.

Ventricular relaxation is an important determinant of both ventricular filling and early diastolic myocardial tension, so that impairment of relaxation has implications for coronary perfusion as well as the global pump function of the heart. These initial results support our hypothesis that enflurane influences diastolic myocardial relaxation and, furthermore, they suggest that when coronary perfusion to a modest proportion of myocardium (27 ± 2% of the total ventricular mass in this case) is critically reduced, this effect is augmented.

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REFERENCES

Cutfield, G. R., Francis, C. M., Foëx, P., Lowenstein, E., Davies, W. L., and Ryder, W. A. (1980). *Br. J. Anaesth.*, **52**, 951P.

Weiss, J. L., Frederiksen, J. W., and Weisfeldt, M. L. (1976). *J. Clin. Invest.*, **58**, 751.

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## THE ASSESSMENT OF REGIONAL MYOCARDIAL CONTRACTILITY: THE USE OF THE END-SYSTOLIC PRESSURE–LENGTH RELATIONSHIP

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The influence of halothane anaesthesia on segmental shortening in the intact heart has been described (Lowenstein et al., 1981). However, no index of regional myocardial contractility is currently available. There is widespread evidence that the end-systolic dimension to which a ventricle contracts is a linearly increasing function of end-systolic pressure (Sagawa, 1978). Recent work has confirmed the linearity of the end-systolic pressure–length (P–$L_{es}$) relationship (Francis, 1981) and has demonstrated that a high level of adrenergic stimulation leads to a marked increase in its slope. This suggests that the P–$L_{es}$ relationship may be a sensitive index of regional myocardial contractility. The study presented here extends these observations by examining the response of the P–$L_{es}$ relationship to moderate increases and decreases in inotropic state.

Two groups of experiments were performed in 12 dogs. In group I ($n = 7$), P–$L_{es}$ relationships were studied under pentobarbitone anaesthesia before and after the infusion of isoprenaline 0.05 $\mu g\,kg^{-1}\,min^{-1}$. The experiments in group II ($n = 5$) were carried out under two levels of halothane anaesthesia (0.75% and 1.25%, inspired concentration). In both groups, each dog was instrumented for the measurement of e.c.g., aortic and left ventricular pressures and aortic flow. Segmental shortening in two areas of the anterior wall of the left ventricle was measured using ultrasonic crystals implanted at the sub-endocardium. The P–$L_{es}$ relationship was determined by infusing phenylephrine 1–8 $\mu g\,kg^{-1}\,min^{-1}$ over 5–10 min so that a smooth increase in aortic pressure was obtained. The data were recorded on magnetic tape and pressure–length loops drawn off line on an $X$–$Y$ recorder. The P–$L_{es}$ points from each phenylephrine challenge were manually digitized and a linear regression calculated.

The data in table VII summarize the experimental observations. In group I, the infusion of isoprenaline led to an increase in LV $dP/dt_{max}$ (+43%) and segmental shortening (+13%) whilst in group II, these indices were depressed by halothane (−27% and −15%, respectively). A change in contractility led to a displacement in the P–$L_{es}$ relationship as indicated by the end-systolic length (ESL) at the beginning of each phenylephrine challenge. The slope of the relationship increased markedly in response to isoprenaline (+61%), but was unchanged by deepening halothane anaesthesia.

This study has demonstrated that, although the P–$L_{es}$ relationship is sensitive to positive inotropic interventions, caution should be applied in using it to quantify the contractile state of depressed hearts.

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REFERENCES

Francis, C. M. (1981). *J. Physiol. (Lond.)*, **320**, 95P.

Lowenstein, E., Foëx, P., Francis, C. M., Davies, W. L., Yusuf, S., and Ryder, W. A. (1981). *Anesthesiology*, **55**, 349.

Sagawa, K. (1978). *Circ. Res.*, **43**, 677.

TABLE VII. *Influence of changes in contractility on myocardial performance (mean ± SEM). Statistical significance symbols refer to paired Student's* t *tests:* *$P < 0.05$; ***$P < 0.005$; ****$P < 0.001$

| | LV $dP/dt_{max}$ ($mm\,Hg\,s^{-1}$) | Shortening (%) | ESL (mm) | P–$L_{es}$ ($mm\,Hg\,mm^{-1}$) |
|---|---|---|---|---|
| Group I | | | | |
| Control | 1800 ± 220 | 19.33 ± 1.52 | 8.05 ± 0.14 | 50.89 ± 3.57 |
| Isoprenaline | 2575 ± 310**** | 21.79 ± 1.75**** | 7.59 ± 0.19*** | 81.91 ± 7.46**** |
| Group II | | | | |
| Control | 1585 ± 135 | 24.12 ± 3.27 | 7.64 ± 0.33 | 57.47 ± 10.64 |
| Halothane | 1150 ± 75* | 20.44 ± 3.05**** | 7.91 ± 0.32**** | 55.40 ± 10.79 |

*Br. J. Anaesth.* (1982), 54, 1143

# CORRESPONDENCE

## PENTOLINIUM IN POSTOPERATIVE HYPERTENSION

Sir,—I was interested in the report by Jones, Hantler and Knight (1981) on the use of pentolinium to control hypertension after operation. Two of the patients described had undergone surgery which could affect the blood supply of the brain and it is on these that I would like to comment. Carotid artery stenosis is often part of bilateral and disseminated vascular disease. Therefore an adequate cerbral blood flow may require a high perfusion pressure, and any reduction in arterial pressure to "normal" values may lead to cerebral ischaemia and thrombosis of the carotid artery. I would agree with control of gross hypertension, but strongly believe that a short-acting drug should be used so that its effects may rapidly reverse in the event of the development of neurological sequelae.

Considering the problems of aneurysm surgery, vasospasm occurs commonly after operation (Fernside and Adams, 1978) and it has reported that there is a steady decrease in cerebral blood flow after subarachnoid haemorrhage (Meyer, Neil-Dwyer and Lowe, 1981). This may result in cerebral ischaemia which will induce reflex hypertension, the effectiveness of which has been indicated by the improvement in cerebral state by induced hypertension in patients with vasospasm (Brown, Hanlon and Mullan, 1978). I accept that control of severe hypertension would benefit the heart, and reduce the formation of cerebral oedema, but unless it is possible to monitor cerebral oxygenation, in my opinion it is unwise to reduce the arterial pressure at all, particularly with a drug which is long acting.

Being a ganglion blocker, one of the side-effects of pentolinium is pupillary dilatation as a result of parasympathetic ganglion blockade (Wade, 1977). One of the principal signs used in the period after operation for monitoring neurosurgical patients is pupil size. Therefore, drug-induced pupillary dilatation in a patient whose cerebral circulation may be jeopardized by the reduction in arterial pressure could make management impossible.

In conclusion, it is potentially dangerous to reduce the arterial pressure in patients with cerebrovascular disease in whom there is no certainty about the arterial pressure required to maintain an adequate blood flow, particularly in those undergoing surgery on intracerebral vessels.

The measurement of central conduction time may allow the onset of cerebral ischaemia to be predicted (Symon et al., 1979). If this technique becomes fully established, only then may it be possible to reduce an increased arterial pressure with a short-acting agent, thereby benefiting the heart whilst ensuring that the brain was not damaged.

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### REFERENCES

Brown, F. D., Hanlon, K., and Mullan, S. (1978). Treatment of aneurysmal hemiplegia with dopamine and mannitol. *J. Neurosurg.*, 49, 525.

Fernside, M. R., and Adams, C. B. T. (1978). Proceedings of the Society of British Neurological Surgeons. *J. Neurol. Neurosurg. Psychiatr.*, 41, 1052.

Jones, R. M., Hantler, C. B., and Knight, P. R. (1981). Use of pentolinium in postoperative hypertension resistant to sodium nitroprusside. *Br. J. Anaesth.*, 53, 1151.

Meyer, C., Neil-Dwyer, G., and Lowe, D. (1981). Proceedings of the Society of British Neurological Surgeons. *J. Neurol. Neurosurg. Psychiatr.*, 44, 370.

Symon, L., Hardgadine, J., Zawirski, M., and Branston, N. (1979). Central conduction time as an index of ischaemia in subarachroid haemorrhage. *J. Neurol. Sci.*, 44, 95.

Wade, A. (1977). *Martindale: The Extra Pharmacepoeia*, 27th edn, p. 672. London: The Pharmaceutical Press.

Sir,—Dr Walters raises a number of points, but principally questions the advisability of reducing arterial pressure in patients after carotid artery or aneurysm surgery.

As Towne and Bernhard (1980) have reported, severe postoperative hypertension following carotid endarterectomy is a common and serious problem, associated with an increased mortality rate and increased occurrence of neurological deficit. This hypertension has been ascribed to baroreceptor dysfunction (Bove et al., 1979). Dr Walters agrees that carotid artery stenosis is often part of bilateral and disseminated vascular disease. In a review of anaesthesia for carotid endarterectomy, Keats (1981) draws attention to the fact that approximately half the mortality from the operation is the result of heart disease, particularly myocardial infarction. Earlier work in the development of carotid endarterectomy focused, as Dr Walters does, on protecting the brain from ischaemic damage, but as Riles, Kopelman and Imparato (1979) have emphasized, this may be at the expense of inducing myocardial ischaemia. Keats' review is a critical appraisal of methods of cerebral protection, and gives a balanced account of the benefits of these and the risks they may involve by causing myocardial ischaemia. He concludes that "Anesthetic management should be directed toward avoidance of both hypotension and hypertension, maintenance of sleeping blood pressure, avoidance of tachycardia and bradycardia and utilising anesthetic agents and adjuvants that would be selected if one assumed all patients undergoing carotid endarterectomy had symptomatic coronary artery disease." This point of view, in contrast to that of Dr Walters, can no longer be considered controversial. Frost (1981), reviewing the care of patients after carotid endarterectomy states "The major cause of serious postoperative morbidity in patients undergoing carotid endarterectomy is myocardial infarction. In addition, hypertension may increase capillary hydrostatic pressure, especially in ischaemic areas of the brain, leading to protein leak, oedema or haemorragic infarction. Thus maintenance of preoperative baseline arterial pressure after surgery is critical." In our original communication the patient's arterial pressure after carotid endarterectomy was 210/120 mm Hg. Dr Walters quibbles with the use of pentolinium, stating that he believes strongly that a short-acting drug should be used so that its effects may be rapidly reversed in the event of the development of neurological sequelae. Although I realize he is making a general observation, he has also completely missed the point of our report. The patient's arterial pressure was

210/120 mm Hg during the infusion of sodium nitroprusside (SNP) $8\,\mu g\,kg^{-1}\,min^{-1}$, used as the first-choice drug to control the postoperative hypertension. The reasons for the resistance to SNP (sympathetic over activity) and the ability of pentolinium to reduce the arterial pressure smoothly (in the patient reported, to 150/85 mm Hg) and interrupt the pathways leading to sympathetic over activity, are the basis of our original communication.

Dr Walters proceeds to consider the problems of aneurysm surgery, and questions the advisability of reducing arterial pressure in patients who may develop the common complication of cerebral arterial spasm. In support of his opinion that arterial pressure should not only be maintained, but perhaps increased, he cites the work of Brown, Hanlon and Mullan (1978). Unlike the situation after carotid artery surgery, the position regarding the control of arterial pressure after aneurysm surgery is more complex. Walter, Neil-Dwyer and Cruickshank (1982) have recently reported the beneficial effects of adrenergic blockade in patients with subarachnoid haemorrhage. Patients received standard management or standard management with alpha- and beta-adrenergic blockade. During the first month, the group treated with adrenergic blockade suffered fewer episodes of clinical deterioration consistent with cerebral arterial spasm and the outcome subsequent to operation was better. In this group, adrenergic blockade was continued after operation; again, among possible mechanisms for the improved outcome, the authors cite the prevention of myocardial infarction. Adrenergic blockade was investigated because of the possible aetiological role played by catecholamines in causing spasm. It is of interest to speculate on a possible role for pentolinium in this respect, as our report has shown how this agent may be used to decrease sympathetic tone. Mullan, Hanlon and Brown (1978) have also reported on the management of berry aneurysms using induced hypotension with ganglion blockade or SNP. Another report by the same investigators (Brown, Hanlon and Mullan, 1978) cited by Dr Walters details four patients in whom an increase in arterial pressure, in the presence of arterial spasm, was associated with clinical improvement. However, these authors do state that the use of hypertensive treatment is unusual. Nevertheless, it does seem likely that, in the presence of established arterial spasm, it would be unwise to reduce the arterial pressure. As in many circumstances in anaesthesia, each case must be judged on its merits with an understanding of the pathophysiology involved. It is possible that control of sympathetic discharge and arterial pressure after operation will reduce the frequency of arterial spasm. In our original communication the patient who had undergone clipping of a cerebral arterial aneurysm was fully conscious and alert with no evidence of arterial spasm. After full consultation with the neurosurgeons involved it was decided that a reduction of arterial pressure would be of benefit.

Finally, Dr Walters makes two specific points about the use of pentolinium. He usefully emphasizes the fact that pentolinium will cause pupil dilatation and that in certain circumstances this may complicate neurological assessment. However, the patients in our report were alert and awake, making unnecessary the use of pupil size to monitor neurological state, although in other circumstances this may be an important consideration. He is also worried about the duration of action of pentolinium. It has been my experience that the cardiovascular effects of the drug can be simply and rapidly reversed by an increase in intravascular volume, should this be found necessary.

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REFERENCES

Bove, E. L., Fry, W. J., Gross, W. S., and Stanley, J. C. (1979). Hypotension and hypertension as consequences of baroreceptor dysfunction following carotid endarterectomy. *Surgery*, 85, 633.

Brown, F. D., Hanlon, K., and Mullan, S. (1978). Treatment of aneurysmal hemiplegia with dopamine and mannitol. *J. Neurosurg.*, 49, 525.

Frost, E. A. M. (1981). Anaesthetic management of cerebrovascular disease. *Br. J. Anaesth.*, 53, 745.

Keats, A. S. (1981). Anesthesia for carotid endarterectomy. *Cleve. Clin. Q.*, 48, 68.

Mullan, S., Hanlon, K., and Brown, F. (1978). Management of 136 consecutive supratentorial berry aneurysms. *J. Neurosurg.*, 49, 794.

Riles, T. S., Kopelman, I., and Imparato, A. M. (1979). Myocardial infarction following carotid endarterectomy; a review of 683 operations. *Surgery*, 85, 249.

Towne, J. B., and Bernhard, V. M. (1980). The relationship of postoperative hypertension to complications following carotid endarterectomy. *Surgery*, 88, 575.

Walter, P., Neil-Dwyer, G., and Cruickshank, J. M. (1982). Beneficial effect of adrenergic blockade in patients with subarachnoid haemorrhage. *Br. Med. J.*, 284, 1661.

## POSTOPERATIVE BUPRENORPHINE

Sir,—In a recent paper, Watson and her colleagues studied the duration of analgesia following two different i.v. doses of buprenorphine in the period immeidately after operation.

This was done by means of a demand-analgesia technique, in which diamorphine was given "on demand" from the 3rd to 12th hours after buprenorphine administration, and the cumulative dose requirements recorded. The results for each group of patients were expressed by a cumulative mean dose plot and analysed by means of linear regression.

While there is no doubt that the cumulative dose plots for the two patients groups are quite different, it is equally clear that the method of analysis is inappropriate.

Linear regression may be applied to a plot of $y$ upon $x$ under defined conditions. First, each value of $y$ (which may be the mean of several estimates) must be independent from those determined at other $x$-loci. Second, the error variance must not differ significantly for all values of $y$.

In this case, neither criterion is satisfied; therefore the analysis is of limited value, since the regression coefficient cannot be compared statistically with that derived from a second set of data.

Since the cumulative doses for two groups of patients at any selected time (say 540 min) may be compared very simply by means of Student's *t* test, the authors do their data an injustice by the uncomprehending use of a more complex method.

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REFERENCE

Watson, P. J. Q., McQuay, H. J., Bullingham, R. E. S., Allen, M, C., and Moore, R. A. (1982). Single-dose comparison of buprenorphine 0.3 and 0.6 mg i.v. given after operation: clinical effects and plasma concentrations. *Br. J. Anaesth.*, 54, 37.

## ADVERSE RESPONSES TO I.V. ANAESTHETICS

Sir,—Shortly after reading Dr Mehta's letter (1981) we had the following unfortunate experience. A 67-year-old male was scheduled for right thoracotomy for recurrent pleural effusion, which was thought likely to be of malignant origin. He had had a bronchoscopy 4 weeks previously (which showed no abnormality), for which he was anaesthetized uneventfully with Althesin 5 mls, diluted to 10 ml with water, and suxamethonium. At the preoperative visit he was in moderate health. The e.c.g. showed left ventricular hypertrophy and slight S–T depression. However, there was no history of any previous illness. His arterial pressure was 140/90 mm HG and his heart rate 120 beat min$^{-1}$. He was given lorazepam 3.5 mg 2 h before operation.

After pre-oxygenation, anaesthesia was induced with Althesin 2.5 ml diluted to 5 ml with water and given slowly, droperidol 20 mg, fentanyl 500 μg and pancuronium 6 mg. After 2 min ventilation with 50% nitrous oxide in oxygen, a slight generalized flush was noted. Bronchoscopy was commenced, ventilation being maintained with a Sanders injector. However, the patient soon became cyanosed and hypotensive and developed a severe bradycardia. Bronchoscopy was abandoned and resuscitative measures commenced. The lungs were easily inflated with no sign of bronchospasm but, in spite of rapid fluid replacement, drug treatment and external cardiac massage, the circulation remained inadequate. Left thoracotomy was performed and internal cardiac massage commenced with an improvement in oxygenation, but not in the size of the pupils, which remained fixed and dilated. At this time it was noted that the left ventricle in particular remained atonic. Internal cardiac massage and supportive measures were continued for 1 h, to no avail.

At postmortem the findings showed a massive left ventricular myocardial infarction, considerable evidence of previous myocardial ischaemia, and severe narrowing of all coronary vessels.

Two blood samples were taken, one into EDTA and one into heparin, 40 min after induction, and sent to Dr J. Watkins at the Supraregional Protein Reference Unit at the Royal Hallamshire Hospital, Sheffield (Watkins, Thornton and Clarke, 1979). These indicated an identical degree of complement C3 conversion around 90% of total, involving excessive activation of the alternative pathway. In the absence of a sequence of samples it was quite impossible to determine whether or not this activation proceeded via an immune-mediated event, that is alternative pathway activation occurring as an enhancement of classical complement activation. However, the previous apparently uneventful exposure to Althesin 4 weeks earlier might well suggest the acquisition of immunological memory to this drug by the patient. Irrespective of the true initiating mechanism, immune or non-immune, this pattern of C3 conversion is consistent with an Althesin reaction (Watkins, 1979) and the degree of conversion would be expected to initiate, through histamine release, a marked degree of hypotension. However, even with this degree of C3 activation, most patients recover rapidly with few side-effects following aggressive therapy. The evidence points to an Althesin-initiated reaction, involving complement, in contrast to pancuronium, which would have been expected to liberate histamine directly.

We feel that this report is important for the following reasons: this is a proven reaction to Althesin in spite of the fact that the drug was diluted, that only a small dose was used and that it was given slowly. The case also underlines the dangers of repeated exposure to the same anaesthetic drug and particularly to the Cremophor – containing drug formulations when these are repeatedly administered at intervals of only a few weeks. In the majority of instances the patient would have been expected to survive but, because of the underlying pathology, even a mild reaction resulted in a fatal outcome.

Althesin is frequently chosen as an induction agent in poor-risk patients, (Dundee and Clarke, 1980). However, these are the very patients who may be least able to withstand even a minor adverse reaction.

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### REFERENCES

Dundee, J. W., and Clarke, R. S. J. (1980). Non-inhalational anaesthetics; in *General Anaesthesia* (Eds T. G. Gray, J. F. Nunn and J. E. Utting), 4th edn, vol. 1, p. 244. London: Butterworth.

Mehta, S. (1981). Adverse responses to i.v. anaesthesia. *Br. J. Anaesth.*, 53, 1005.

Watkins, J. (1979). Anaphylactoid reaction to i.v. substances. *Br. J. Anaesth.*, 51, 51.

——Thornton, J. A., and Clarke, R. S. J. (1979). Adverse reactions to i.v. agents. *Br. J. Anaesth.*, 51, 469.

## CYANIDE RELEASE FROM NITROPRUSSIDE

Sir,—We hasten to take issue with the recent report by Bisset and others (1981) before some innocent patient is placed in jeopardy by a physician who accepts it at face value.

They suggest that there is "no unambiguous evidence that cyanide is released from nitroprusside *in vivo*". Workers too numerous to cite exhaustively here have contributed positive findings in patients and in laboratory animals to the contrary. In the interests of conserving space I will review only our personal experience (Smith and Kruszyna, 1974). Mice and rats given acute lethal doses of nitroprusside exhibit classic signs of cyanide poisoning, have lethal concentrations of cyanide in their blood at death, and are protected against death by two cyanide antagonists with independent mechanisms of action, namely nitrite and thiosulphate.

If Bisset and his colleagues (1981) are correct, there are two possible interpretations of these results. First, the solutions of nitroprusside, freshly prepared before injection, had already undergone complete photolytic decomposition to cyanide before they were even administered. A critical observation suggests that that was not the case. Animals injected with cyanide as such invariably die in less than 5 min, whereas in animals given nitroprusside, death was delayed for an average of 30 min, indicating a critical time-dependent phenomenon was required *in vivo* for conversion of nitroprusside to cyanide. We reiterate our conviction that this phenomenon involves a direct chemical redox reaction between nitroprusside and haemoglobin. The alternative explanation which Bisset would have us accept is that the blood cyanide measured was generated artefactually during the analytical procedure. If such was the case, it is difficult to rationalize how or why the animals died and how or why cyanide antagonists protected them against death.

Quite aside from cyanide analyses, we have demonstrated spectrophotometrically (Smith and Kruszyna, 1974) a direct chemical reaction between nitroprusside and haemoglobin both aerobically and anaerobically, in which the product is cyanmethaemoglobin. Obviously, such a product can only arise by oxidation of the ferrous haem groups of haemoglobin. We have postulated a direct exchange of electrons from nitroprusside to ferrous haem groups by analogy with the well-known reaction between ferricyanide and haemoglobin. If dithionite is also present, the product is nitric oxide haemoglobin.

We have found large differences in the rates of cyanide release when nitroprusside was incubated with red cells from various laboratory species, differences in the rates of cyanide release between red cell suspensions and lysates, and differences in rates of cyanide release between red cell suspensions, suspensions of their membranes (ghosts) and solutions of glutathione. These differences were found in experiments which were all conducted under identical conditions of ambient illumination. If cyanide release were a result only of photolytic decomposition of nitroprusside during the analytical procedure, no such differences should have been found.

We are at a loss to explain the failure of Bisset and his colleagues (1981) to confirm these results which have, at least in part, been confirmed many times over by others. We have, of course, tested nitroprusside as such in our analytical procedure for cyanide and obtained values comparable to those found with saline. A possible explanation for one of their experiments occurs to us, namely the failure of blood to accelerate cyanide release from nitroprusside in solutions at pH 4.0. Depending on ionic strength and buffer capacity, solutions of such acid pH would be expected to lyse red cells, denature haemoglobin and generate methaemoglobin or acid haematin. Methaemoglobin is not reactive toward nitroprusside, which is in accord with our hypothetical mechanism (Smith and Kruszyna, 1974).

Bisset and colleagues (1981) have performed a service in reminding us that, under some conditions, nitroprusside may undergo photolytic decomposition so that precautions to protect solutions against ambient illumination are only prudent. To suggest, however, that "it may well be safe to infuse quantities (. . of nitroprusside . .) larger than those currently recommended" is to invite disaster.

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REFERENCES

Bisset, W. I. K., Butler, A. R., Glidewell, C., and Reglinski, J. (1981). Sodium nitroprusside and cyanide release: Reasons for re-appraisal. *Br. J. Anaesth.*, 53, 1015.

Smith, R. P., and Kruszyna, H. (1974). Nitroprusside produces cyanide poisoning *via* a reaction with hemoglobin. *J. Pharmacol. Exp. Ther.*, 191, 557.

## HUNTINGTON'S CHOREA

Sir,—I was interested to read the letter from Drs Browne and Cross (1981) on Huntington's Chorea. In earlier years, Tasmania was regarded as having the greatest frequency (seven per 100 000) in the world. I discussed (Lamont, 1979) the previous case reports by Davies (1966), Farina and Rauscher (1977), Gualandi and Bonfanti (1968) and concluded by asking if relaxants of either the depolarizing or the non-depolarizing types be used "carte blanche". Subsequently, at a meeting of the Royal College of Surgeons of Australasia in Hobart, I presented a short paper entitled "Huntington's Chorea—Is there an Anaesthetic Problem?" Arising from this paper, two points of significance emerged.

First, with the advent of CAT Scanning it is clear that a number of patients with Huntington's Chorea may have considerable hydrocephalus. This may account for dose-dependent depression of cerebral metabolism leading to respiratory depression.

Second Whittaker (1980), in her recent article indicated that patients with Huntington's disease could have a greater frequency of the rare $E_1^f$ gene; thus the anaesthetist simply requesting a dibucaine number guarding against the possibility of apnoea, may overlook the presence of the other variant. Browne and Cross did, in fact, perform the fluoride estimation.

Third, using a peripheral nerve stimulator in a small number of patients, I have been able to obtain a satisfactory train-of-four together with fade and tetanus.

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REFERENCES

Browne, M. G., and Cross, R. (1981). Huntington's Chorea. *Br. J. Anaesth.*, 53, 1367.

Davies, D. D. (1966). Abnormal response to anaesthesia in a case of Huntington's Chorea. *Br. J. Anaesth.*, 38, 490.

Farina, J., and Rauscher, L. A. (1977). Anaesthesia and Huntington's Chorea. A report of two cases. *Br. J. Anaesth.*, 49, 1167.

Gualandi, W., and Bonfanti, G. (1968). A case of prolonged apnoea in Huntington's Chorea. *Acta Anaesthesiol. (Padova)*, 19, (Suppl. 6), 235.

Lamont, A. S. M. (1979). Anaesthesia and Huntington's Chorea. *Anaesth. Intens. Care*, 7, 189.

Whittaker, M. (1980). Plasma cholinesterase variants and the anaesthetist. *Anaesthesia*, 35, 174.

## EXTRADURAL BUPRENORPHINE

Sir,—We would like to comment on a letter from Christensen and Andersen (1982) regarding extradural buprenorphine which, unfortunately, leaves some misinterpretations of the literature, including our own. Buprenorhphine is a new narcotic analgesic acting as a partial agonist. Contrary to the opinion of Christensen and Andersen, the opiate agonist–antagonist group is known to be associated with respiratory depression similar to that produced by morphine when given in therapeutic doses i.m. or i.v. The carbon dioxide response curve is depressed by 42% with morphine (Weil et al., 1975), by 46% with pentazocine (Malischewski, Sybrecht and Fabel, 1980) and by 27% with buprenorphine (Klose, Ehrhart and Jung, 1982). The time-course of respiratory depression shows a more prolonged displacement of the carbon dioxide response curve with buprenorphine compared with morphine (Orwin, Orwin and Price, 1976). In an unpublished investigation on the respiratory depressant effects of extradural buprenorphine we have seen carbon dioxide response curves similar to those in an earlier study on extradural morphine. It is important to mention that all these studies were performed on pain-free patients. We suggest that, in clinical practice, when a narcotic analgesic is given for example to abolish upper abdominal pain, there is even an increase in respiratory function. This was demonstrated by Bromage, Camporesi and Chestnut (1980) for both i.v. and extradural morphine. Christensen and Andersen used extradural buprenorphine, because two patients developed tolerance to extradural morphine. We have not observed tolerance in the first 40 patients with cancer treated with extradural morphine (Zenz, Scheppler-Scheele et al., 1981). We have now treated 93 patients suffering from advanced cancer pain with extradural opiates, 15 patients being treated for more than 100 days and two patients for more than 300 days. Our observations have not changed. The increased need for narcotics, given systemically or extradurally, in our opinion is a result of the continuing infiltration of cancer in the terminal stage, and this is in accordance with the wide experience of Twycross (1975).

Concerning the side-effects of extradural buprenorphine, we do not agree with the conclusions of the Danish group. The observed signs (low arterial pressure, increased heart rate, pale and cold skin) are not typical signs of opiate intoxication. There was no miosis, no respiratory depression, no sedation. Perhaps these signs were the result of an opiate withdrawal syndrome following the change of an opiate agonist to a partial agonist.

In our studies of more than 5000 single injections we have never observed these haemodynamic changes after extradural opiates. Furthermore, the total frequency of side-effects was significantly lower with extradural buprenorphine than with morphine. This is the result of a double-blind study published elsewhere (Zenz, Piepenbrock et al., 1981), which is confirmed by our clinical observation in cancer pain treatment. In six of the 93 patients we changed therapy from morphine to buprenorphine because there were side-effects like vomiting, urinary retention and constipation. Only one of these patients also had side-effects with extradural buprenorphine. This observation is in accordance with the physico-chemical properties of the substance. Buprenorphine, being highly lipid-soluble is washed out rapidly from the c.s.f. In contrast, water-soluble drugs like morphine will linger in the c.s.f. and may be carried cephalad. In this way the most severe side-effect of extradural opiates — respiratory depression — is more likely to be caused by morphine than by buprenorphine. This is also the conclusion of Bromage (1981) and de Castro and Lecron (1981) recommending the use of lipid-soluble drugs for extradural injection.

Concerning an eventual neurotoxic effect of extradural opiates, very little is known. Engquist (1981) reported that the postmortem histological investigation of some 30 patients after long treatment with extradural morphine revealed no neurotoxic effect on nerve roots, or spinal cord.

Although we have seen more side-effects after extradural morphine than after buprenorphine, we do not conclude that extradural morphine should not be used. It has been a great support for many thousands of postoperative patients and cancer patients, but our own experiences and physio-chemical data result in our preference for buprenorphine.

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REFERENCES

Bromage, P. R. (1981). The price of intraspinal narcotic analgesia: basic constraints. *Aneth. Analg. (Cleve.)*, **60**, 461.

—— Camporese, E., and Chestnut, D. (1980). Epidural narcotics for postoperative and analgesia. *Anesth. Analg. (Cleve.)*, 59, 473.

de Castro, J., and Lecron, L. (1981). Peridurale Opiate-Analgesie; verschiedene Opiate – Komplikationen und Nebenwirkungen; in *Peridurale Opiate-Analgesie* (ed. M. Zenz). Stuttgart: Fischer.

Christensen, F. R., and Andersen, L. W. (1982). Adverse reaction to extradural buprenorphine. *Br. J. Anaesth.*, **54**, 476.

Engquist, A. (1981). Grundlagen der periduralen Opiate-Analgesie und Klinische Erfahrungen; in *Peridurale Opiat-Analgesie* (ed. M. Zenz). Stuttgart: Fischer.

Klose, R., Ehrhart, A., and Jung, R. (1982). Der Einfluß von Buprenorphin und Tramadol auf die $CO_2$-Antwort in der unmittelbar postoperativen Phase nach Allgemeinanästhesie. *Anästh. Intensivther Notfallmed.*, 17, 29.

Malischewski, C. M., Sybrecht, G. W., and Fabel, H. (1980). Einfluß von starken Analgetika auf den Mundokklusionsdruck und die ventilatorische $CO_2$-Antwort. *Anästh. Intensivther. Notfallmed.*, 15, 470.

Orwin, J. M., Orwin, J., and Price, M. (1976). A double-blind comparison of buprenorphine and morphine in conscious subjects following administration by the intramuscular route. *Acta Anaesthesiol. Belg.*, 3, 171.

Twycross, R. G. (1975). The use of narcotic analgesics in terminal illness. *J. Med. Ethics*, **1**, 10.

Weil, J. W., McCullough, R. E., Kline, J. S., and Sodal, I. E. (1975). Diminished ventilatory response to hypoxia after morphine in normal man. *N. Engl. J. Med.*, **292**, 1103.

Zenz, M., Piepenbrock, S., Hübner, B., and Glocke, M. (1981). Peridurale Analgesie mit Buprenorphin und Morphin bei postoperativen Schmerzen. *Anästh. Intensivther. Notfallmed.*, **16**, 333.

—— Schappler-Scheele, B., Neuhaus, R., Piepenbrock, S., and Hilfrich, J. (1981). Long-term peridural morphine analgesia in cancer pain. *Lancet*, **1**, 91.

# BOOK REVIEW

*Neural Blockade in Clinical Anesthesia and Management of Pain.* Edited by M. J. Cousins and P. O. Bridenbaugh. Published (1980) by Harper & Row Ltd. Pp. 749; illustrated; indexed. Price £62.00.

Every journal editor is aware of the vast number of books on anaesthesia flooding on to the market. Such large numbers inevitably result in a reduction in overall standard and blunt the excitement which one likes to feel on being asked to review a new product. I am happy to record, however, that *Neural Blockade* is one of the more welcome newcomers of recent years. Professors Cousins and Bridenbaugh have brought together some 40 experts on various aspects of the physiology, pharmacology and clinical practice of neural blockade in a most readable and elegant volume of more than 700 pages. I commend particularly the historical introduction by B. R. Fink, and G. T. Tucker and L. E. Mather on the Absorption and Disposition of Local Anaesthetics.

The main section of the work (Techniques of Neural Blockade) is a detailed but well laid out practical guide. There is less scope for originality in this part, indeed some of the authors have—correctly, in my view—drawn on illustrations from earlier publications, notably the elegant drawings by Miss McLarty for the handbooks produced many years ago by Sir Robert Mackintosh. Nevertheless, I believe that this part of the book will become the principal reference source on its subject in the foreseeable future.

The third section of the book, on pain therapy, is the least consistent part of the work in respect of quality of presentation. It is also likely to become out of date faster. Others, including some of the present authors, have done equally well elsewhere. This section could have been abandoned without loss in my view.

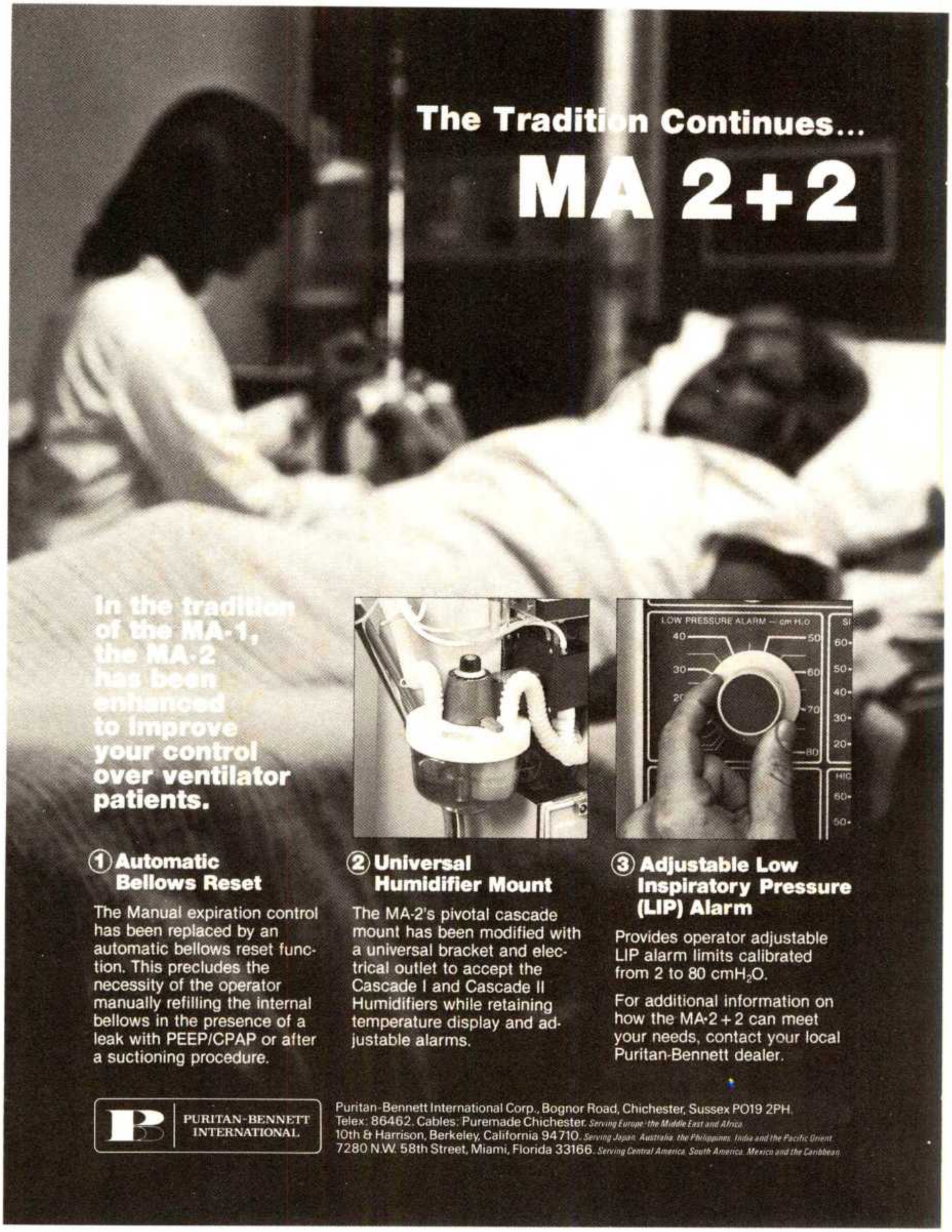
Publishers hint that it is less than sophisticated for a reviewer to comment on the price of a book. In spite of that I should like to comment on the price of this one. I am not suggesting for one minute that the publishers or authors are sequestering disproportionate profits, for I have no knowledge of that. I do know, however, that colour printing is expensive and that it has been used to little useful effect in this book. Although various companies have been thanked for their help with colour printing one is left wondering if a black-and-white edition would not almost certainly have been a better buy.

*Alastair A. Spence*

OTHER BOOKS RECEIVED

*Infectious Diseases in General Medical Practice.* By Joseph Marr. Published by Addison-Wesley Publishing. Pp. 460; illustrated; indexed. Price $29.95.

*Psychosocial Aspects of Medical Practice: Children and Adolescents.* By Robert O. Pasnau. Published by Addison-Wesley Publishing. Pp. 320; indexed. Price $26.95.



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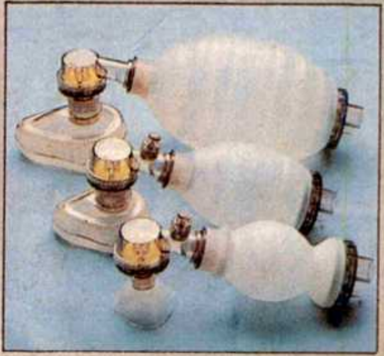

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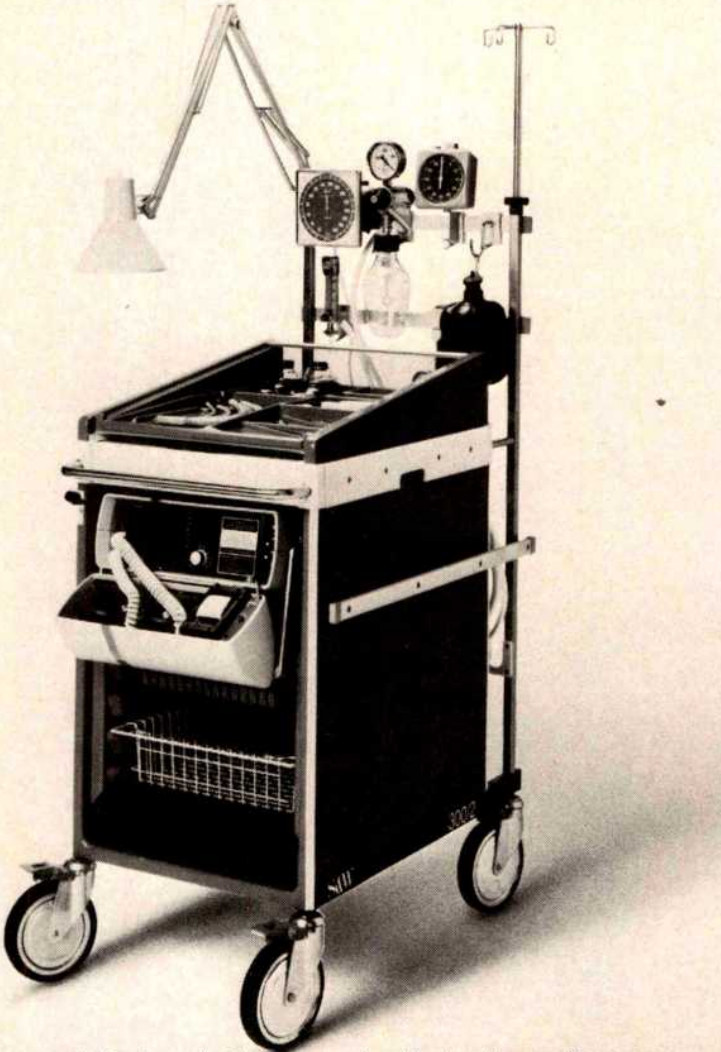

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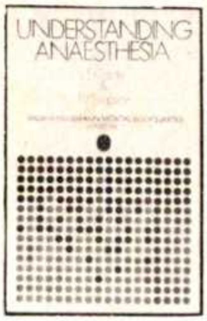

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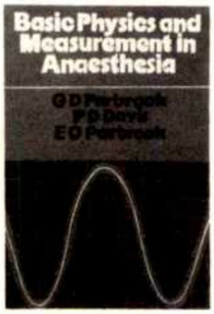

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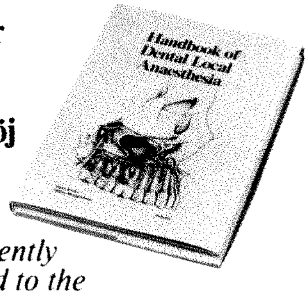

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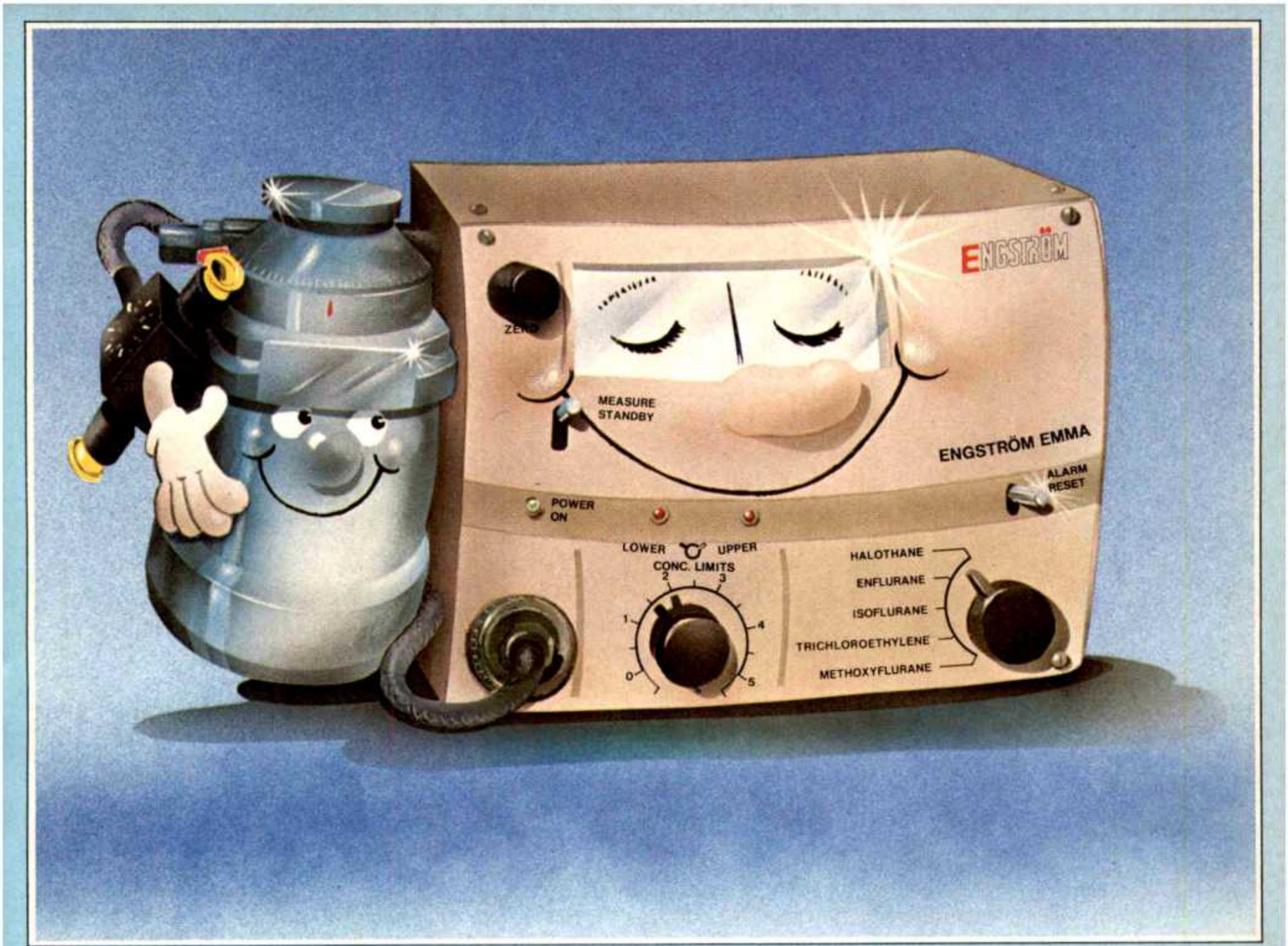

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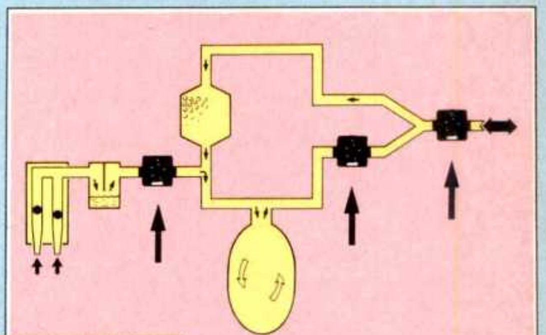

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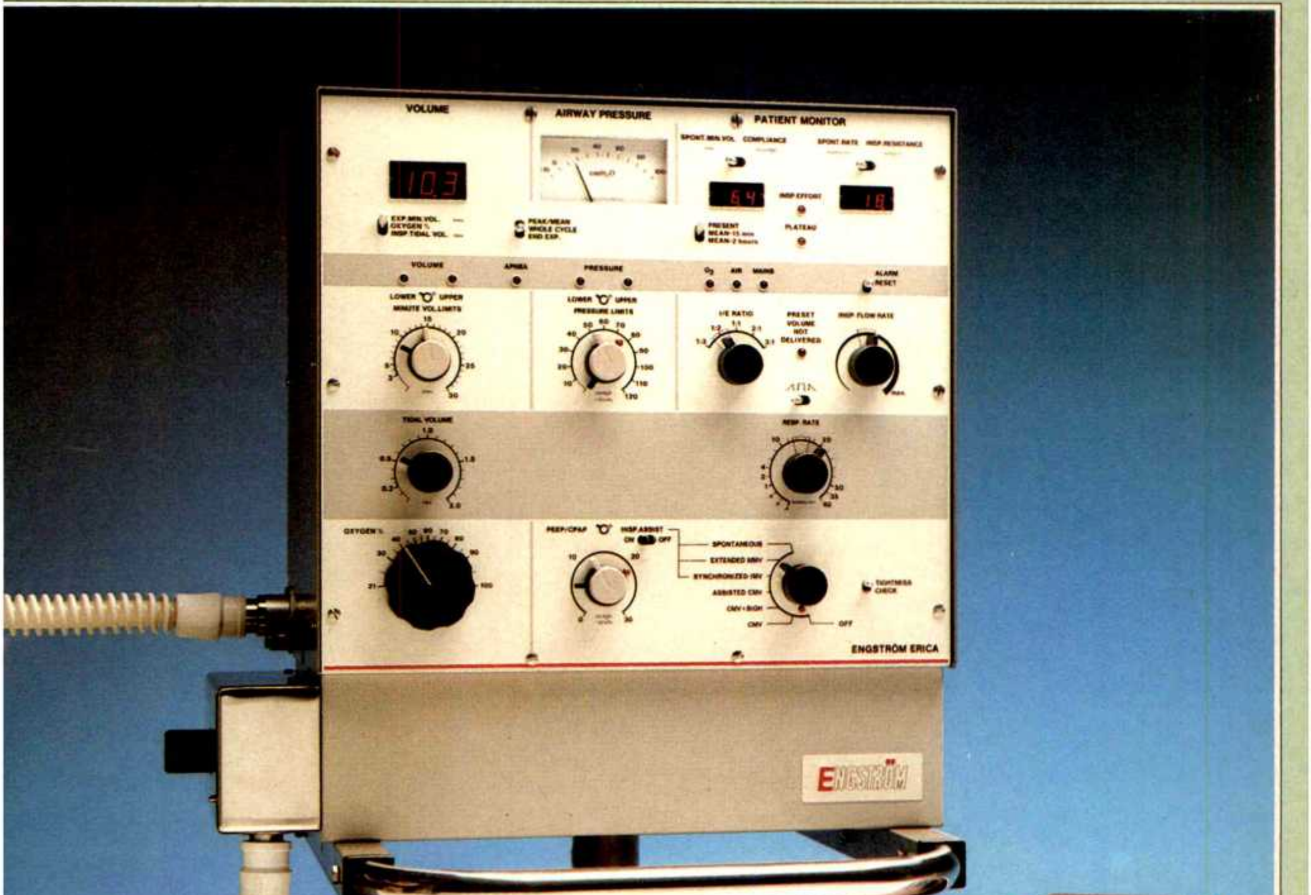

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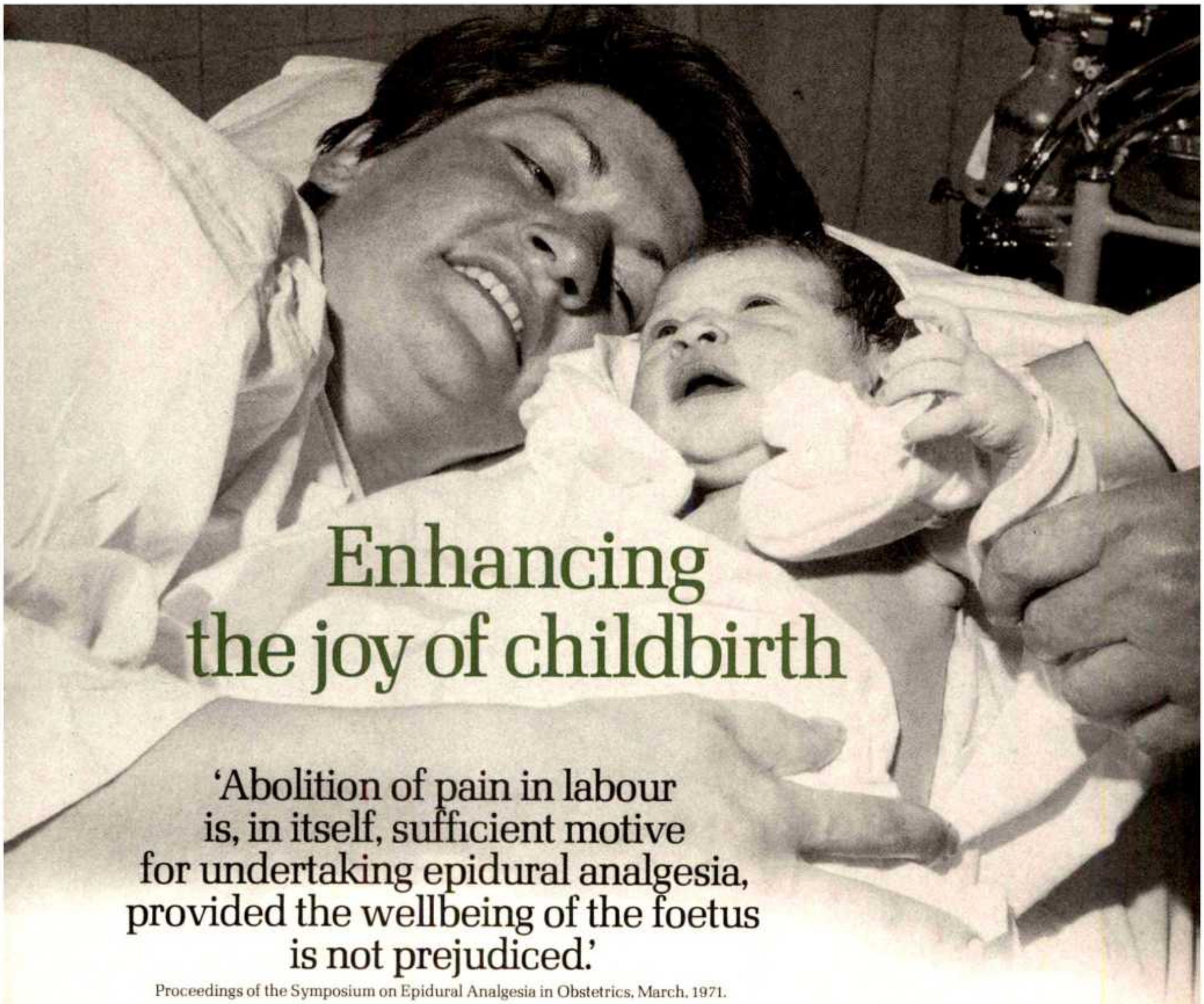

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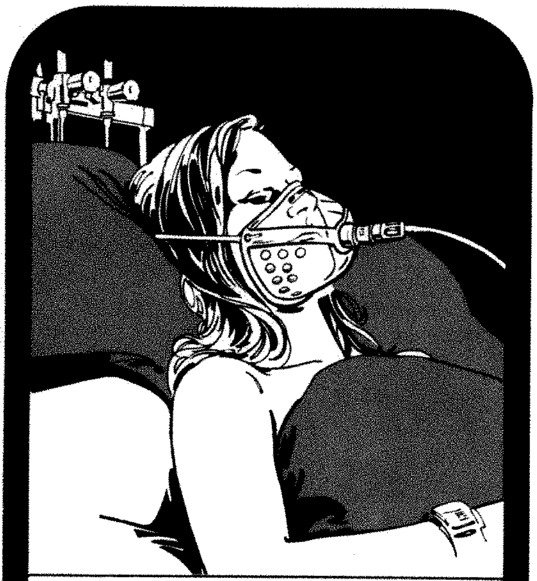

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*1. Cox D, Gillbe C, 'Fixed Performance Oxygen Masks' Hypoxic hazard of low capacity designs. Anaesthesia, 1981, Volume 36, pages 958-964

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# EDITORIAL

## OPIOID ANAESTHESIA—FACT OR FALLACY?

It is now 13 years since the observations of Lowenstein and others (1969) that large doses of morphine produced minimal haemodynamic disturbances when given as a sedative to patients requiring prolonged artificial ventilation. They also showed that morphine 0.5–3.0 mg kg$^{-1}$ given as a sole agent provided stable anaesthesia for cardiac surgery. As a consequence morphine and, more recently, fentanyl have been widely used for cardiac anaesthesia. It is now appropriate to assess the status of this type of anaesthesia.

The apparent cardiovascular stability obtained with morphine anaesthesia for valve surgery was less obvious when this technique was used for coronary artery surgery, with hypotension, hypertension, vasodilatation (from histamine release) and an unacceptable frequency of awareness (Lowenstein, 1971; Rosow et al., 1982). Because of the high degree of cardiovascular stability obtained with large doses of fentanyl (1–2 mg kg$^{-1}$) in the dog (Liu et al., 1976) it was used as an alternative to morphine anaesthesia for both mitral valve and coronary artery operations (Stanley and Webster, 1978; Lunn et al., 1979). The cardiovascular stability obtained with fentanyl 60–70 $\mu$g kg$^{-1}$, particularly during induction and tracheal intubation, even in patients with limited cardiac reserve, has been a main attraction of this technique to cardiac anaesthetists (Sebel et al., 1982; Zurik et al., 1982).

However, cardiovascular problems can occur during opioid anaesthesia. Bradycardia is a well known side-effect of opioids, but can be minimized with atropine (Stanley and Webster, 1978) or with pancuronium (Sebel et al., 1982). More troublesome is the occurrence of hypertension which is observed in the period following sternotomy (Edde, 1981). This is more common in patients with coronary artery disease in whom hypertension, resulting in increased heart work and oxygen consumption, is potentially dangerous. These patients have limited ability to increase coronary artery blood flow and a large increase in arterial pressure can compromise their myocardial oxygen supply/demand balance (Waller and Kaplan, 1981). With doses of fentanyl 60–70 $\mu$g kg$^{-1}$ there is a 45–50% frequency of hypertension greater than 20% of the pre-induction value (Sebel et al., 1982); increasing the dose to 125 $\mu$g kg$^{-1}$ reduces the frequency to 10% (de Lange, Stanley and Boscoe, 1980). Our own observations are that the most potent stimulus causing hypertension is surgical manipulation of the aortic root and we suggest that this is a result of stimulation of a specific cardiac chemoreflex, possibly involving the chemoreceptor described by James, Isobe and Urthaler (1975). Increased plasma catecholamines (Sebel et al., 1981a) or light anaesthesia (Sebel et al., 1981b) do not appear to play a part in this hypertensive response.

Inadequate anaesthesia and a high frequency of awareness was a major disadvantage of morphine anaesthesia (Lowenstein, 1971). This problem does not appear to be as prevalent when fentanyl is used. Despite the widespread use of this anaesthetic technique, particularly in the U.S.A., there have been only isolated reports of awareness (Mummaneni, Rao and Montoya, 1980; Hilgenberg, 1981). Although the true frequency of awareness during fentanyl anaesthesia is unknown, the reported frequency compares favourably with inhalation techniques.

Another potential advantage of opioid anaesthetic techniques is the reduction in metabolic and stress responses to surgery (Hall, 1980; Sebel et al.,

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1981a). Although theoretically beneficial, it has never been demonstrated that this produces a clinical advantage to the patient.

There are currently two schools of thought on the best anaesthetic technique for cardiac anaesthesia: inhalation or i.v. The myocardial depressant action of inhalation drugs has generally been considered a disadvantage in patients with limited cardiovascular reserve. While this may be true for the more severely ill patient, there is recent evidence to suggest that halothane increases coronary vascular reserve (Merin, 1980) and may thus be beneficial for the ischaemic heart. Waller and Kaplan (1981) recommended the use of inhalation drugs, which produce controllable myocardial depression, for patients with good left ventricular function undergoing coronary artery surgery, and the use of opioids for patients with diminished cardiac reserve. It is likely that the cardiac anaesthetist of the future may be more selective in his choice of anaesthetic technique based on improved pharmacological data. There is a definite need for large well-controlled clinical trials comparing the two methods of anaesthesia; opioid *v.* inhalation.

In our opinion, opioid anaesthesia has an important role in the anaesthetic management of the cardiac patient. The lack of cardiovascular depression and the attenuation of metabolic responses are potentially most beneficial in patients with severely compromised left ventricular function.

*P.S. Sebel and J.G. Bovill*

## REFERENCES

Edde, R. R. (1981). Hemodynamic changes prior to and after sternotomy in patients anaesthetised with high-dose fentanyl. *Anesthesiology,* 55, 444.

Hall, G. M. (1980). Fentanyl and the metabolic response to surgery. *Br. J. Anaesth.,* 52, 561.

Hilgenberg, J. C. (1981). Intraoperative awareness during high-dose fentanyl oxygen anesthesia. *Anesthesiology,* 54, 341.

James, T. N., Isobe, J. H., and Urthaler, F. (1975). Analysis of components in a cardiogenic hypertensive reflex. *Circulation,* 52, 179.

Lange, S. de, Stanley, T. H., and Boscoe, M. J. (1980). Fentanyl–oxygen anaesthesia: comparison of anaesthetic requirements and cardiovascular responses in Salt Lake City, Utah and Leiden, the Netherlands. 7th World Congress of Anaestesiologists Hamburg, F.R.G. Amsterdam: *Excerpta Medica,* Abstract no. 646, p. 313.

Liu, W. S., Bidwai, A. W., Stanley, T. H., and Isern-Aramel, J. (1976). Cardiovascular dynamics after large doses of fentanyl and fentanyl plus nitrous oxide in the dog. *Anesth. Analg. (Cleve),* 55, 168.

Lowenstein, E. (1971). Morphine anesthesia—a perspective. *Anesthesiology,* 35, 563.

—— Hallowell, P., Levine, F. H., Daggett, W. M., Austin, G., and Laver, M. B. (1969). Cardiovascular responses to large doses of intravenous morphine in man. *N. Engl. J. Med.,* 281, 1389.

Lunn, J. K., Stanley, T. H., Eisler, J., Webster, L., and Woodward, A. (1979). High-dose fentanyl anesthesia for coronary artery sugery: plasma fentanyl concentrations and influence of nitrous oxide on cardiovascular responses. *Anesth. Analg. (Cleve.),* 58, 390.

Merin, R. G. (1981). Is anesthesia beneficial for the ischemic heart? *Anesthesiology,* 55, 341.

Mummaneni, N., Rao, T. L. K., and Montoya, A. (1980). Awareness and recall with high-dose fentanyl–oxygen anesthesia. *Anesth. Analg. (Cleve.),* 59, 948.

Rosow, C. E., Moss, J., Philbin, D. M., and Savarese, J. J. (1982). Histamine release during morphine and fentanyl anesthesia. *Anesthesiology,* 56, 93.

Sebel, P. S., Bovill, J. G., Schellekens, A. P. M., and Hawker, C. D. (1981a). Hormonal responses to high-dose fentanyl anaesthesia. *Br. J. Anaesth.* 53, 941.

—— —— Wauquier, A., and Rog, P. (1981b). Effects of high-dose anesthesia on the electroencephalogram. *Anesthesiology,* 55, 203.

—— —— Boekhorst, R. A. A., and Rog, N. (1982). Cardiovascular effects of high-dose fentanyl anaesthesia. *Acta Anaesthesiol. Scand.,* 26, 308.

Stanley, T. H., and Webster, L. R. (1978). Anesthetic requirements and cardiovascular effects of fentanyl–oxygen and fentanyl–diazepam–oxygen anesthesia in man. *Anesth. Analg. (Cleve.),* 57, 411.

Waller, J. L., and Kaplan, J. A. (1981). Anaesthesia for patients with coronary artery disease. *Br. J. Anaesth.,* 53, 757.

Zurick, A. M., Urzua, J., Yared, J.-P., and Estafanous, F. G. (1982). Comparison of hemodynamic and hormonal effects of large single-dose fentanyl anesthesia and halothane/nitrous oxide anesthesia for coronary artery surgery. *Anesth. Analg. (Cleve.),* 61, 521.

Br. J. Anaesth. (1982), 54, 1151

# REPETITIVE ADMINISTRATION OF PANCURONIUM AND VECURONIUM (Org NC 45, NORCURON) IN PATIENTS UNDERGOING LONG LASTING OPERATIONS

W. BUZELLO AND G. NÖLDGE

## SUMMARY

Fifty-one patients undergoing surgical procedures which required at least 2 h of anaesthesia were randomly divided into two groups receiving either pancuronium or vecuronium (Org NC 45) as a muscle relaxant under evoked twitch tension control. In the absence of halogenated inhalation anaesthetics, both drugs were administered by initial bolus injection of 0.1 mg $kg^{-1}$, followed by increments of 0.025 mg $kg^{-1}$ when twitch height had recovered to 25% of control. In all cases the initial dose produced total neuromuscular blockade and satisfactory intubation conditions within 2–4 min. The time of onset was slightly shorter with vecuronium than with pancuronium. The mean duration from the end of injection to 25% recovery of the initial and the maintenance doses was three and four times longer with pancuronium than with vecuronium, respectively. The average drug requirement per hour to maintain at least 75% block was one maintenance dose of pancuronium 0.025 mg $kg^{-1}$ and four maintenance doses of vecuronium 0.1 mg $kg^{-1}$. The overall recovery time (25% to 75% twitch height) irrespective of the number of maintenance doses was 40 ± 14 min with pancuronium and 15 ± 8 min with vecuronium (mean ± SD). Some cumulation was observed with pancuronium, particularly in terms of prolonged recovery time. With vecuronium, both duration of action of maintenance doses and recovery time did not depend on the number of maintenance doses. In both groups of patients no cardiovascular or other side-effects were observed. It is concluded that vecuronium is a true intermediate-acting non-depolarizing muscle relaxant. Its lack of cumulation favours the maintenance of profound neuromuscular blockade until close to the end of operation without the risk of an unduly long recovery time.

In addition to atracurium (Payne and Hughes, 1981), pipecurium (Classen and Schramm, 1980), the "bulky esters" (Savarese and Wastila, 1979) and chandonium (Gandiha, Marshall and Paul, 1975), vecuronium (Org NC 45, Norcuron) represents one of the recent approaches to develop a muscle relaxant meeting the requirements listed in table I. Chemically, vecuronium is a monoquaternary pancuronium analogue. After favourable results of both animal experiments and clinical pilot studies (Bowman and Norman, 1980) the drug has now been subjected to a multi-centre clinical trial. In this context the present paper reports a comparative study of repetitive administration of pancuronium and vecuronium in long-lasting operations.

## PATIENTS AND METHODS

Fifty-one adult patients of both sexes, ASA class I–II, undergoing surgical procedures requiring at least 2 h of anaesthesia were investigated. Informed consent had been obtained in all cases. The patients were randomly divided into two groups receiving either pancuronium ($n = 22$) or vecuronium ($n = 29$) as muscle relaxant. Patients under 20 and over 60 yr of age and those with neuromuscular, renal and hepatic disease were excluded from the study.

All patients were premedicated with atropine 0.01 mg $kg^{-1}$, fentanyl 0.0015 mg $kg^{-1}$ and droperidol 0.07 mg $kg^{-1}$ i.m. Anaesthesia was induced with thiopentone 200–300 mg, fentanyl 0.3–0.5 mg and droperidol 5–10 mg. The trachea was intubated after muscle relaxation with pan-

TABLE I. *Properties desirable in an ideal muscle relaxant (Savarese and Kitz, 1973)*

| | |
|---|---|
| (1) | Rapid onset of action (30–45 s) |
| (2) | Short duration of block (10–20 min) |
| (3) | No cumulative effects |
| (4) | Reversal of block by suitable antidote |
| (5) | No pharmacologically active or toxic metabolites |
| (6) | High potency |
| (7) | No histamine release |
| (8) | No cardiovascular side-effects |

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curonium 0.1 mg kg$^{-1}$ or vecuronium without the aid of suxamethonium. Anaesthésia was maintained with increments of fentanyl according to the individual requirements under mechanical ventilation with oxygen in nitrous oxide 1:2 in the absence of halogenated inhalation anaesthetics. One-quarter of the initial dose of the appropriate muscle relaxant was repeated when neuromuscular transmission had recovered 25% of control. Neuromuscular function was assessed by recording evoked twitch tension of the adductor pollicis muscle. Train-of-four supramaximal square pulses (0.2 ms, 2 Hz, 30 s apart) were delivered to the ulnar nerve at the wrist by a battery-operated Myotest nerve stimulator (Viby-Mogensen et al., 1980). The resulting twitch tension was quantitated by a boomerang force displacement transducer (Walts, Lebowitz and Dillon, 1968) and recorded on a polygraph. Table II gives the parameters taken from the tracings. Recovery time was measured in both the absence and presence of neostigmine. In the latter conditions (eight patients receiving pancuronium and eight receiving vecuronium) neostigmine 0.02 mg kg$^{-1}$ was administered with atropine 0.015 mg kg$^{-1}$ when twitch tension had recovered 25% of control. In seven patients who received pancuronium and eight who received vecuronium, recovery time was not measured because these patients were either transferred to the intensive care unit for mechanical ventilation before twitch tension had recovered 75% of control, or neostigmine had been given at a later stage of recovery than 25% twitch height.

Clinical observations included intubation conditions, arterial pressure (RIVA-ROCCI), heart rate, e.c.g., and signs of histamine release (skin reactions, bronchoconstriction).

All variables were calculated as means and standard deviations ($\bar{x} \pm$ SD). Student's *t* test was used to assess statistical significance. Linear regressions were calculated after the least squares method.

TABLE II. *Variables of time course of neuromuscular blockade*

| | |
|---|---|
| Onset | Time from end of injection to maximum block |
| $\mathrm{DUR}_{25}$ | Duration from end of injection of initial dose to 25% recovery |
| $\mathrm{DUR}_{90}$ | Duration from end of injection of initial dose to 90% recovery |
| $\mathrm{DUR}_{\mathrm{rep}.25}$ | Duration from end of injection of maintenance dose to 25% recovery |
| Recovery time | Time from 25% to 75% recovery after the last maintenance dose or after the initial dose in the absence of maintenance doses |

## RESULTS

The duration of anaesthesia was 161 ± 47 and 171 ± 76 min in the pancuronium and vecuronium group, respectively. In all cases the initial doses of both muscle relaxants produced total neuromuscular blockade with smooth intubation conditions. Particularly with vecuronium, it was our experience that in some patients the muscles of the vocal cords were completely paralysed when active movement of the arms and hands was still present. Cardiovascular side-effects, skin reactions and bronchoconstriction did not occur.

The variables describing the time course of neuromuscular blockade produced by pancuronium and vecuronium are summarized by figure 1. Additionally, figure 2 shows the evoked mechanomyograms of one representative case from each group. In detail, the following results were obtained:

(i) The *time of onset* tended to be shorter with vecuronium than with pancuronium (3.5 ± 2.7 *v.* 2.5 ± 1 min without statistical significance).

(ii) The *mean duration of the initial dose* ($\mathrm{DUR}_{25}$) was three times longer with pancuronium than with vecuronium; this was statistically significant.

(iii) The requirement of *maintenance doses* is illustrated in table III. Nearly a quarter of the patients who received pancuronium did not need any maintenance dose and, with one exception only, not more than three increments had to be given to the remaining 16 patients. Mean $\mathrm{DUR}_{\mathrm{rep}.25}$ ranged between 20 and 150 min. In the vecuronium group, 70% of patients required five to 15 maintenance doses. Accordingly, $\mathrm{DUR}_{\mathrm{rep}.25}$ ranged between 8 and 25 min which is about one-quarter of that of pancuronium. On average, one maintenance dose of pancuronium or four maintenance doses of vecuronium per hour were required to maintain neuromuscular transmission less than 25% of control (0.015 *v.* 0.10 mg kg$^{-1}$ h$^{-1}$). Some *cumulation*, in terms of increasing duration of action with increasing number of maintenance doses, may be suspected from three patients of four who received three or more maintenance doses of pancuronium and from eight patients of 28 receiving up to nine maintenance doses of vecuronium (table IV). However, this tendency is not reflected by the overall values of figure 1.

(iv) In the pancuronium group the *recovery time* irrespective of the previous number of maintenance doses (fig. 1) was 40 ± 14 min ($n = 7$) in the absence, and 11 ± 4 min in the presence of neostigmine ($n = 8$). With vecuronium, the corresponding fig-

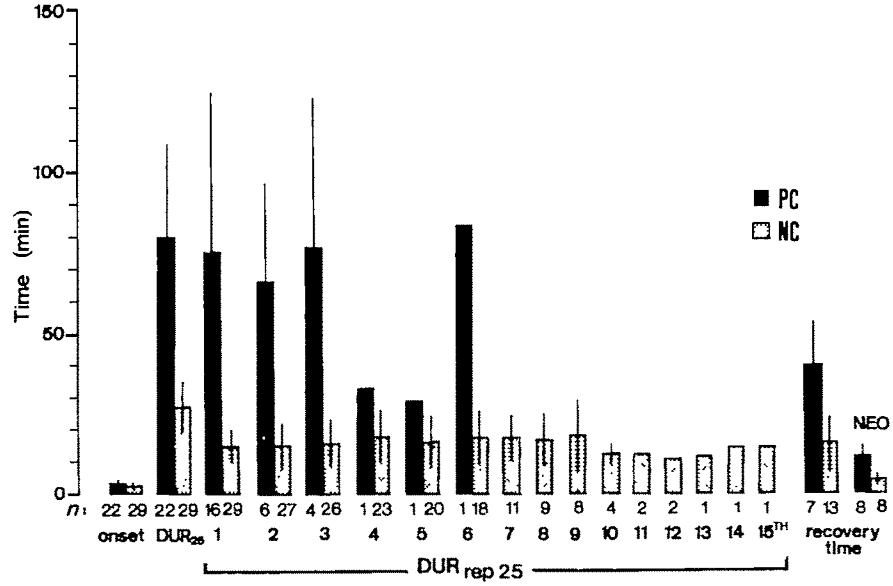

FIG. 1. Time course of neuromuscular blockade (mean ± SD) from repetitive administration of pancuronium (PC) and vecuronium (NC). NEO = recovery time after neostigmine 0.02 mg $kg^{-1}$ given at 25% recovery. $n$ = number of patients.

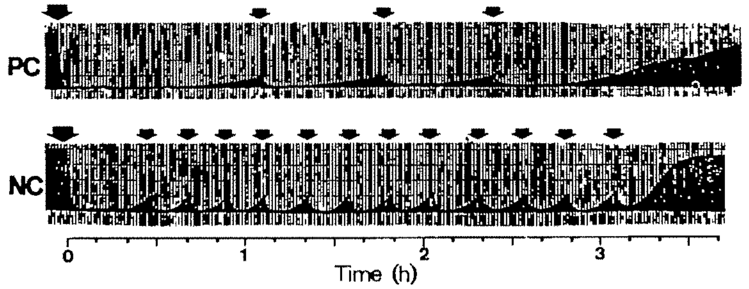

FIG. 2. Representative tracings of neuromuscular blockade from repetitive administration of pancuronium (PC) and vecuronium (NC). Large arrows = 0.1 mg $kg^{-1}$; small arrows = 0.025 mg $kg^{-1}$.

TABLE III. *Distribution of numbers of maintenance doses of pancuronium (PC) and vecuronium (NC). $DUR_{an}$ = duration of anaesthesia (min) (mean ± SD);* n = *number of patients*

| | Number of maintenance doses | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Drug | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 9 | 10 | 12 | 15 | Total |
| PC | | | | | | | | | | | | | |
| *n* | 5 | 11 | 2 | 3 | | | 1 | | | | | | 22 |
| % | 22.7 | 50 | 9 | 13.6 | | | 4.5 | | | | | | 100 |
| $DUR_{an}$ | 134±30 | 179±70 | 272 | 387±162 | | | 265 | | | | | | 161±4 |
| NC | | | | | | | | | | | | | |
| *n* | | 2 | 1 | 3 | 2 | 3 | 6 | 4 | 4 | 2 | 1 | 1 | 29 |
| % | | 6.9 | 3.4 | 10.4 | 6.9 | 10.4 | 20.7 | 13.8 | 13.8 | 6.9 | 3.4 | 3.4 | 100 |
| $DUR_{an}$ | | 125 | 195 | 105±21 | 105 | 220±83 | 143±46 | 115±84 | 233±80 | 163 | 220 | 200 | 174±75 |

TABLE IV. *Patients with increasing duration of action of pancuronium (PC) and vecuronium (NC) associated with increasing number of maintenance doses*

| Relaxant drug | Duration of anaesthesia (min) | $DUR_{25}$ (min) | $DUR_{rep.25}$ (min) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| PC | 480 | 119 | 53 | 93 | 118 | | | | | | |
| | 265 | 43 | 19 | 34 | 26 | 33 | 29 | 83 | | | |
| | 200 | 60 | 37 | 51 | 49 | | | | | | |
| NC | 201 | 26 | 14 | 12 | 16 | 19 | 17 | 18 | 23 | | |
| | 240 | 25 | 17 | 15 | 13 | 16 | 14 | 15 | 16 | 19 | 29 |
| | 195 | 34 | 18 | 10 | 14 | 38 | 35 | 32 | | | |
| | 425 | 24 | 16 | 13 | 18 | 26 | 17 | 35 | | | |
| | 300 | 16 | 10 | 13 | 17 | 20 | 20 | 18 | 18 | 23 | 30 |
| | 315 | 46 | 23 | 40 | 46 | 38 | | | | | |
| | 360 | 25 | 15 | 12 | 16 | 19 | 17 | 23 | 28 | | |
| | 165 | 24 | 13 | 11 | 15 | 27 | 28 | | | | |

ures were 15 ± 8 min ($n = 12$) and 4 ± 2 min ($n = 8$), that is 2.7 and 2.0 times shorter than with pancuronium. Figure 3 illustrates the recovery time as a function of the number of maintenance doses: With pancuronium there is a positive correlation both with and without the interference of neostigmine. In the absence of the reversal agent, three maintenance doses created twice as long a recovery time than the initial bolus alone. A similar correlation exists after reversal of the block by neostigmine. Contrary to pancuronium, there is no such correlation with vecuronium.

## DISCUSSION

The data presented in this paper demonstrate, that vecuronium has a significantly shorter duration of action and recovery time than pancuronium and that it does not significantly accumulate with repetitive administration. These findings are in agreement with those of Agoston and others (1980). After the same initial dose of vecuronium, these authors found a mean time of onset of 2.2 min, $DUR_{25}$ of 26.5 min and a fairly constant $DUR_{rep.25}$ of 19 min while repeating one-half of the initial dose. The mean recovery time was 17 min.

Comparative clinical studies on pancuronium and vecuronium were published by Crul and Booij (1980), Fahey and colleagues (1981b) and Kalina and others (1981). Although their doses were different from ours, Crul and Booij found a slightly shorter time of onset, $DUR_{90}$ twice as long, and three times the recovery time with pancuronium

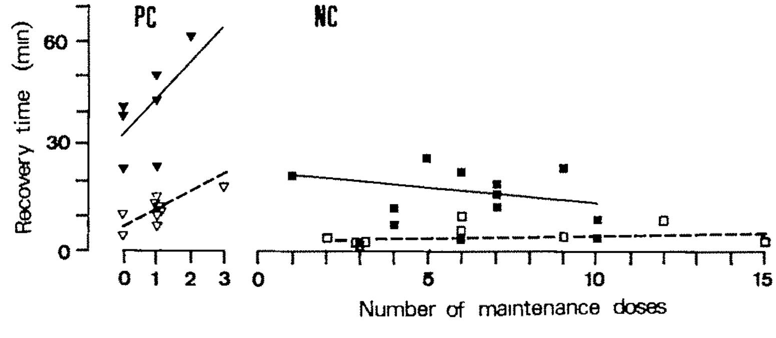

FIG. 3. Linear regression analysis of recovery time as a function of the number of maintenance doses of pancuronium (PC) and vecuronium (NC). ▼——= pancuronium, spontaneous recovery: $r = 0.6, P < 0.1$; ▽---= pancuronium, antagonism with neostigmine (NEO) 0.02 mg kg$^{-1}$ at 25% recovery: $r = 0.8, P < 0.05$; ■——= vecuronium, spontaneous recovery: $r = 0.3$, n.s.; □---= vecuronium, antagonism with neostigmine 0.02 mg kg$^{-1}$ at 25% recovery. Significant correlations with pancuronium, no correlation with vecuronium.

compared with vecuronium. The effect of repetitive administration was not studied systematically.

In the present study as in previous investigations (Crul and Booij, 1980; Fahey et al., 1981b; Kalina et al., 1981) both drugs were administered in equal doses on a mg per kg basis. Recent findings in man indicate that vecuronium is 1.3 to 1.7 times more potent than pancuronium (Buzello et al., 1980; Crul and Booij, 1980; Krieg, Crul and Booij, 1980). Hence, the slightly shorter time of onset of vecuronium which was also reported by Crul and Booij (1980), Agoston and colleagues (1980) and Krieg, Crul and Booij (1980), may be the result of some relative overdosage. In itself, the 2.5 min onset time of vecuronium is not very attractive clinically, because it is still considerably longer than that of suxamethonium. However, the onset of action may be accelerated by increasing the initial dose which, contrary to pancuronium, is unlikely to prolong the recovery time significantly. Further investigation is required to decide whether, in crash induction, vecuronium may become an alternative to suxamethonium.

Excessive individual variation is a common problem in the clinical use of non-depolarizing muscle relaxants (Katz, 1967). This is reflected by the large relative standard deviations of both $DUR_{25}$ and $DUR_{rep.25}$ of pancuronium, ranging between ± 18 and ± 63% of the mean (fig. 1). In absolute figures, $\bar{x} \pm SD$ covers a range from 30 to 90 min. With vecuronium, too, the relative standard deviations may exceed ±50% of the mean. However, in absolute terms, this represents a range as little as 10–15 min, which is not likely to create major clinical problems in the period immediately after anaesthesia.

*Cumulation* of successive doses is a regular finding when pancuronium or other traditional curare derivatives are used. With pancuronium, Fahey and others (1981b) found an increasing duration of block as a result of repeated administration of up to four 0.02-mg $kg^{-1}$ doses. This phenomenon was minimal or absent if vecuronium was given, even in up to five doses of 0.04 mg $kg^{-1}$ each. In the study of Kalina and colleagues (1981), in which both pancuronium and vecuronium were administered in a 0.05-mg $kg^{-1}$ initial bolus followed by increments of 0.015 mg $kg^{-1}$ at 25% recovery, $DUR_{rep.25}$ of both drugs remained fairly constant (about 20–25 min with pancuronium and 10 min with vecuronium), and no signs of cumulation were noticed. In the present study, with twice the initial and maintenance doses, we found moderate cumulation with pancuronium, namely in terms of prolonged recovery time, and no cumulation with vecuronium (fig. 2). Apparently, with pancuronium the evidence of cumulation is dose-dependent, and 0.015–0.025 mg $kg^{-1}$ $h^{-1}$ represents the maintenance dose of a 75% block. This is different with vecuronium which, even in greater doses, does not accumulate. Buzello and others (1980) reported that, after recovery from a 0.075 mg $kg^{-1}$ bolus followed by 10 maintenance doses (0.015 mg $kg^{-1}$ each), another 0.0375 mg $kg^{-1}$ dose produced only 33 min ($DUR_{25}$) neuromuscular block, which was not different in duration from that after a single 0.075-mg $kg^{-1}$ dose. In the present study no signs of cumulation were seen up to a total dose of 0.5 mg $kg^{-1}$ (= 38 mg) of vecuronium within 3 h 20 min (= 9.4 mg $h^{-1}$). In the patients listed in table IV, systemic or local hypothermia may have contributed to the increasing duration of block.

The particular kinetic properties of vecuronium induced neuromuscular blockade are readily explained by the high plasma clearance of the drug 123 ± 41 ml $min^{-1}$ (Somogyi, Shanks and Triggs, 1976). The reason for the rapid decay of the plasma concentration of vecuronium is still unknown. Five (McLeod, Watson and Rawlins, 1976) and 123 ± 41 ml $min^{-1}$ (Somogyi, and Triggs, 1976). The reason for the rapid decay of the plasma concentration of vecuronium is still unknown. Five possible mechanisms have to be discussed: renal and biliary elimination, metabolic and chemical degradation, and redistribution. Although vecuronium has not been determined in the urine, renal excretion can be excluded as a principle limiting the duration of block, since Fahey and others (1981a) found almost equal plasma clearances in anephric and normal patients. The monoquaternary structure of vecuronium renders the molecule less polar than its bisquaternary analogue pancuronium. This may favour its biliary excretion. For pancuronium, this pathway only accounts for about 10% of the administered dose during 24 h (Agoston et al., 1973; Buzello, 1975) and does not contribute to the plasma clearance during spontaneous recovery of neuromuscular transmission under ordinary clinical conditions. It appears reasonable to assume that with vecuronium, even the possibly increased biliary excretion is still far from influencing the duration of block. The same has to be expected from metabolic 3- and 17-desacetylation which for pancuronium accounts for only 10% of the dose during the first 6 h after administration (Agoston et al., 1973; Buzello, 1975). Savage, Sleigh and Carlyle (1980) advocated pH-dependent chemical hydrolysis of the acetyl groups because of the monoquaternary structure of the molecule as a pathway of particular relevance for the pharmacokinetics of vecuronium. In man its role has still to be investigated. The last possible principle is the uptake of the drug by inactive tissues. In kinetic terms this requires a very large total volume of distribution. A synthesis of the findings of McLeod, Watson and Rawlins (1976) and Somogyi, Shanks and Triggs (1976) on pancuronium and Van der Veen and Bencini (1980) and Fahey and colleagues (1981a) on vecuronium does not support this view, since the total volumes of distribution of both drugs are not significantly different. Further investigations in the field of pharmacokinetics and drug metabolism are required to elucidate the fate of vecuronium in man.

*Recovery time* is an index with major clinical implications, because neuromuscular transmission between 25 and 75% represents a stage between acceptable surgical conditions (twitch tension <25%) and full recovery, which in most instances is unsatisfactory for both the surgeon and the anaesthetist. Therefore, for the ideal muscle relaxant, the recovery time should be as short as possible and not depend on the dose. Pancuronium does not meet this requirement. Recovery time after one single $0.1\text{-mg kg}^{-1}$ bolus is 34 ± 10 min, and it may increase over 50 min with the second maintenance dose (table IV). In contrast, vecuronium offers the advantage of a very small level of residual neuromuscular transmission by numerous maintenance doses until close to the end of surgery while still keeping the recovery time as brief as 10–25 min. This property, together with the short $\mathrm{DUR}_{\mathrm{rep.25}}$, suggests the infusion technique as a convenient mode of administration. This technique is now under investigation in our department.

We conclude that, in comparison with pancuronium, the introduction of vecuronium represents a remarkable step toward the "ideal muscle relaxant" according to table I. It is not yet the "non-depolarizing suxamethonium", but in our experience it is the first true intermediate-acting non-depolarizing muscle relaxant which will certainly fill a gap in the anaesthetist's neuromuscular armamentarium.

## REFERENCES

Agoston S., Salt, P., Newton, D., Bencini, A., Boomsma, P., and Erdmann, W. (1980). The neuromuscular blocking activities of Org NC45, a new pancuronium derivative in anaesthetized patients. *Br. J. Anaesth.*, 52, 53S.

——Vermeer, G. A., Kersten, U. W., and Meijer, D. K. F. (1973). The fate of pancuronium bromide in man. *Acta Anaesthesiol. Scand.*, 17, 267.

Bowman, W. C., and Norman, J. (eds) (1980). Symposium on Org NC45. *Br. J. Anaesth.*, 52, (Suppl. 1).

Buzello, W. (1975). Der Stoffwechsel von Pancuronium beim Menschen. *Anaesthesist.*, 24, 13.

——Bischoff, G., Kuhls, E., and Nöldge, G. (1980). The new non-depolarizing muscle relaxant Org NC45 in clinical anaesthesia: preliminary results. *Br. J. Anaesth.*, 52, 62S.

Classen, H. G., and Schramm, V. (eds) (1980). Pipecurium bromide (Arduan). *Drug. Res.*, 1, 341.

Crul, J. F., and Booij, L. D. H. J. (1980). First clinical experiences with Org NC45. *Br. J. Anaesth.*, 52, 49S.

Fahey, M. R., Morris, R. B., Miller, R. D., Nguyen, T. L., and Upton, R. A. (1981a). Pharmacokinetics of Org NC45 (Norcuron) in patients with and without renal failure. *Br. J. Anaesth.*, 53, 1049.

————Sohn, Y. J., Cronelly, R., and Gencarelli, P. (1981b). Clinical pharmacology of Org NC45 (Norcuron). *Anesthesiology.*, 55, 6.

Gandiha, A., Marshall, I. G., and Paul, D. (1975). Some actions of chandonium iodide, a new short acting muscle relaxant, in anaesthetized cats and on the isolated muscle preparation. *Clin. Exp. Pharm. Physiol.*, 2, 159.

Kalina, K., Fitzal, S., Schwarz, S., Zadrobilek, E., and Steinbereithner, K. (1981). Erste Ergebnisse einer Vergleichsstudie von Org NC45 und Pancuronium. Proceedings, 10th International Anaesthesia Postgraduate Course, Vienna, 1981, p. 87.

Katz, R. L. (1967). Neuromuscular and electromyographic effects of d-tubocurarine, edrophonium and neostigmine in man. *Anesthesiology.*, 28, 327.

Krieg, N., Crul, J. F., and Booij, L. H. D. J. (1980). Relative potency of Org NC45, pancuronium, alcuronium and tubocurarine in anaesthetized man. *Br. J. Anaesth.*, 52, 783.

McLeod, K., Watson, M. J., and Rawlins, M. D. (1976). Pharmacokinetics of pancuronium in patients with normal and impaired renal function. *Br. J. Anaesth.*, 48, 341.

Payne, J. P., and Hughes, R. (1981). Evaluation of atracurium in anaesthetized man. *Br. J. Anaesth.*, 53, 45.

Savage, D. S., Sleigh, T., and Carlyle, I. (1980). The emergence of Org NC45, 1- (2, 3, 5, 16, 17) -3, 17-bis (acetyloxy)-2-(1-piperidinyl)-androstan-16-yl) -1-methylpiperidinium bromide, from the pancuronium series. *Br. J. Anaesth.*, 52, 3S.

Savarese, J. J., and Kitz, R. J. (1973). The quest for a short-acting non-depolarizing neuromuscular blocking agent. *Acta Anaesthesiol. Scand.* (Suppl.) 53, 43.

——Wastila, W. B. (1979). Pharmacology of BW785U: a short-acting non-depolarizing neuromuscular blocking agent. *Anesthesiology*, 51, S277.

Somogyi, A. A., Shanks, C. A., and Triggs, E. J. (1976). Clinical pharmacokinetics of pancuronium bromide. *Eur. J. Clin. Pharmacol.*, 10, 367.

Van der Veen, F., and Bencini, A. (1980). Pharmacokinetics and pharmacodynamics of Org NC45 in man. *Br. J. Anaesth.*, 52, 37S.

Viby-Mogensen, J., Hansen, P. H., Jørgensen, B. C., Ørding, H., Kann, T., and Fries, B. (1980). A new nerve stimulator (Myotest). *Br. J. Anaesth.*, 52, 547.

Walts, L. F., Lebowitz, M., and Dillon, J. B. (1968). A means of recording force thumb adduction. *Anesthesiology*, 29, 1054.

## ADMINISTRATIONS REPETEES DE PANCURONIUM ET DE VECURONIUM (ORG NC45, NORCURON) CHEZ DES PATIENTS SOUMIS A DES INTERVENTIONS DE LONGUE DUREE

### RESUME

Cinquante et un patients adultes subissant des actes chirurgicaux, qui nécessitaient au moins 2 h d'anesthésie, ont été divisés au hasard en deux groupes recevant soit du pancuronium soit du vécuronium (Org NC 45) comme myorelaxant, sous surveillance de la pression provoquée par le twitch. En l'absence d'anesthésiques halogénés inhalés, les deux agents étaient administrés avec une injection directe initiale de 0,1 mg kg$^{-1}$ suivie d'injections complémentaires de 0,025 mg kg$^{-1}$ lorsque la hauteur du twitch était revenue à 25% de la valeur témoin. Dans tous les cas, la dose initiale a entraîné un block neuromuscularie complet et des conditions d'intubation satisfaisantes en 2–4 min. Le délai d'installation était légèrement plus bref avec le vecuronium qu'avec le pancuronium. La durée moyenne comprise entre la fin de l'injection et la récupération de 25% du twitch avec injection de la dose d'entretien était trois à quatre fois plus longue avec le pancuronium qu'avec le vecuronium. La dose de produit moyenne nécessaire par heure pour maintenir un block d'au moins 75% était une dose d'entretien de pancuronium (0,025 mg kg$^{-1}$) et quatre doses d'entretien de vecuronium (0,1 mg kg$^{-1}$). Le temps de récupération globale (25 à 75% de hauteur du twitch) était 40 ± 14 min avec le pancuronium et 15 ± 8 min avec le vecuronium quel qu'ait été le nombre des réinjections. Une certaine accumulation a été observée avec le pancuronium, particulièrement en termes de prolongation du temps de récupération. Avec le vecuronium, ni la durée d'action de la dose d'entretien ni le temps de récupération ne dépendraient du nombre de doses d'entretien. Dans aucun des groupes n'ont été observés d'effets secondaires cardiovasculaires ou autres. Nous en concluons que le vécuronium est un agent myorelaxant non dépolarisant vraiment intermédiaire. L'absence d'accumulation favorise la maintenance d'un bloc neuromusculaire profond presque jusqu'à la fin de l'intervention sans risque de réveil indûment retardé.

## REPETITIVE ANWENDUNG VON PANCURONIUM UND VECURONIUM (ORG NC 45, NORCURON) BEI PATIENTEN MIT LANGDAUERNDEN OPERATIONEN

### ZUSAMMENFASSUNG

Fünfzig erwachsene Patienten, die sich Operationen unter mindestens 2 Stunden dauernder Narkose unterzogen, wurden radomisiert in zwei Gruppen aufgeteilt. Von ihnen erhielt die eine Pancuronium and die andere Vecuronium (Org NC 45) als Muskelrelaxans. Die neuromuskuläre Übertragung wurde durch das evozierte Mechanomyogramm überwacht. Halogenierte Inhalationsnarkotika wurden nicht verwandt. Beide Muskelrelaxantien wurden in gleicher Dosierung verabreicht, und zwar in Form eines initialen Bolus von 0,1 mg kg$^{-1}$ gefolgt von Widerholungsdosen von 0,025 mg kg$^{-1}$ bei Erholung der Kontraktionskraft auf 25% der Kontrollwerte. In allen Fällen führte die Initialdosis innerhalb 2–4 Minuten bei totaler neuromuskulärer Blockade zu guten Intubationsbedingungen. Vecuronium hatte eine etwas kürzere Anschlagszeit als Pancuronium. Die mittlere Wirkungsdauer der Initial- bzw. Erhaltungsdosen, gerechnet vom Ende der Injektion bis 25% Erholung, was nach Pancuronium drei- bzw. viermal länger als nach Vecuronium. Der durchschnittliche stündliche Relaxansbedarf zur Aufrechterhaltung einer mindestens 75%igen neuromuskulären Blockade betrug eine Erhaltungsdosis Pancuronium (0,025 mg kg$^{-1}$) bzw. vier Erhaltungsdosen Vecuronium (0,1 mg kg$^{-1}$). Die Erholungszeit (Zeit von 25 bis 75% Erholung) ohne Rücksicht auf die Anzahl der vorangegangenen Erhaltungsdosen betrug bei Pancuronium 40 ± 14 Minuten und bei Vecuronium 15 ± 8 Minuten ($\bar{x} \pm$ SD). Eine geringe Kumulation wurde bei Pancuronium beobachtet, vorrangig in Form einer verlängerten Erholungszeit. Bei Vecuronium ließ weder die Wirkungsdauer der Erhaltungsdosen noch die Dauer der Erholungszeit eine Abhängigkeit von der Anzahl der Erhaltungsdosen erkennen. Cardiovaskuläre oder andere Nebenwirkungen wurden in keiner Patientengruppe beobachtet. Vecuronium kann hiernach als ein wirkiches mittellang wirksames Muskelrelaxans eingestuft werden. Das weitgehende Fehlen von Kumulationserscheinungen begünstigt die Aufrechterhaltung einer tiefen Muskelrelaxation nahezu bis zum Operationsende ohne die Gefahr einer übermäßig langen Erholungszeit. Die Substanz ist allerdings nicht so kurz wirksam, daß sie Succinylcholin vollständig ersetzen könnte.

## ADMINISTRACIÓN REPETIDA DE PANCURONIO Y DE VECURONIO (ORG NC 45, NORCURON) A PACIENTES SOMETIDOS A OPERACIONES DE LARGA DURACIÓN

### SUMARIO

Se repartió al azar cincuenta y un pacientes adultos sometidos a operaciones quirúrgicas que necesitaban por lo menos 2 h de anestesia en dos grupos a los cuales se administró ya sea pancuronio ya sea vecuronio (Org NC 45) como relajante muscular bajo control de tensión de contracción evocada. En la ausencia de anestéticos halogenados de inhalación, se administró ambas substancias mediante una inyección de bolo inicial de 0,1 mg kg$^{-1}$, seguida por incrementos de 0,025 mg kg$^{-1}$, cuando el tope de la contracción había vuelto al 25% del control. En todos los casos, la dosis inicial produjo un bloqueo neuromuscular total y condiciones de intubación satisfactorias dentro de 2–4 min. El momento en que se inició la acción del vecuronio se produjo ligeramente más rápido que para el pancuronio. El periodo medio que media entre el fin de la inyección y una recuperación del 25% de las dosis iniciales y de mantenimiento fue tres y cuatro veces más largo con el pancuronio que con el vecuronio, respectivamente. La cantidad media de dichas substancias que se necesitaba cada hora para mantener un bloqueo de por lo menos un 75% correspondía a una dosis de mantenimiento de pancuronio (0,025 mg kg$^{-1}$) y cuatro dosis de mantenimiento de vecuronio (0,1 mg kg$^{-1}$). El tiempo global de recuperación (25% al 75% del tope de contracción), sin tener en cuenta el número de dosis de mantenimiento, fue de 40 ± 14 min con el pancuronio y de 15 ± 8 min con el vecuronio (media ± SD). Se observó alguna acumulación con el pancuronio, en particular en cuanto a la prolongación del periodo de recuperación. En lo que se refiere al vecuronio, tanto la duración de acción de las dosis de mantenimiento como el tiempo de recuperación no dependieron del número de dosis de mantenimiento. En ambos grupos de pacientes, no se observó ningún efecto secundario cardiovascular o de otra índole. Se concluye que el vecuronio constituye un verdadero relajante muscular nodepolarizante de acción intermedia. Su falta de acumulación propicia el mantenimiento de un bloqueo neuromuscular profundo hasta casí el fin de la operación sin el riesgo de causar un periodo de recuperación demasiado largo.

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# CLINICAL STUDIES ON ORG NC 45: COMPARISON WITH PANCURONIUM

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SUMMARY

Some actions of Org NC 45 have been compared with those of pancuronium in a study on 50 patients anaesthetized with nitrous oxide and narcotic supplements. The train-of-four technique was used to assess the recovery of neuromuscular blockade and its antagonism. Org NC 45 was shown to have a duration of action from injection of the intubating dose ($0.1 \text{ mg kg}^{-1}$) to the reappearance of the first twitch response of 23.5 ± 1.1 min; the corresponding time for pancuronium $0.1 \text{ mg kg}^{-1}$ was 50.5 ± 3.6 min. Recovery time from the initial incremental dose to the reappearance of the first train-of-four response was 11.6 ± 0.8 min with Org NC 45 and 31 ± 4.7 min with pancuronium. No evidence of cumulation was seen following several incremental doses of Org NC 45. The rate of onset of paralysis of adductor pollicis was faster with Org NC 45 than with pancuronium, but the difference did not reach statistical significance. Satisfactory spontaneous recovery from Org NC 45 blockade could be achieved without undue delay. Org NC 45 was shown to produce significantly less tachycardia.

The animal pharmacology of Org NC 45 was described by Durant and his co-workers (Durant et al., 1979; Durant, Houwertjes and Crul, 1980). Further animal studies, and the preliminary clinical reports were the subject of a symposium, the proceedings of which were edited by Bowman and Norman (1980).

In man Org NC 45 has a potency slightly greater than, and a duration of action one-half to one-third that of pancuronium. There is a rapid offset of action and little or no cumulation following multiple doses. The neuromuscular blockade is easily antagonized by neostigmine. There is no evidence of cardiovascular side-effects even at doses in excess of those required to ensure good muscle relaxation during surgery.

These clinical characteristics have been confirmed by Fahey and others (1981), who concluded that Org NC 45 warrants further investigation since it appears to offer advantages over the currently available neuromuscular blocking drugs.

The present study compares aspects of the pharmacological profile of Org NC 45 with those of pancuronium when used in approximately equipotent doses for tracheal intubation and for muscle relaxation.

## METHODS

Fifty healthy patients undergoing elective surgery requiring muscle relaxation were studied. Written consent for the study was obtained from each patient.

Each patient was randomly assigned to one of two groups to receive Org NC 45 $0.1 \text{ mg kg}^{-1}$ or pancuronium $0.1 \text{ mg kg}^{-1}$. These doses were selected because Agoston and others (1980) considered that the potency of Org NC 45 approximated to that of pancuronium in anaesthetized patients. The anaesthetic technique was otherwise identical for each group. I.m. premedication was either morphine 10 mg and atropine 0.6 mg, or papaveretum 15–20 mg and hyoscine 0.3–0.4 mg, given approximately 1 h before induction of anaesthesia. An i.v. infusion of Ringer's lactate solution was commenced. Anaesthesia was induced with droperidol 5–10 mg and fentanyl 0.1–0.15 mg given into the infusion, followed 5 min later by a dose of thiopentone sufficient to induce sleep (200–400 mg). Injection of the neuromuscular blocker followed immediately and tracheal intubation was performed 90 s later. Anaesthesia was maintained with 66% nitrous oxide in oxygen and increments of fentanyl were given as required. The lungs were ventilated artificially. Heart rate and arterial systolic pressure were measured throughout using a Roche 105 E.C.G. monitor and a sphygmomanometer respectively. Neuromuscular transmission was monitored

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using a Myotest peripheral nerve stimulator (Viby-Mogensen, Hansen et al., 1980) surface electrodes being placed over the ulnar nerve at the right wrist. A train-of-four stimulus (Ali, Utting and Gray, 1971) was given with tactile evaluation of the evoked response of adductor pollicis, the same investigator (W.B.) making the assessment on every occasion.

The elapsed time between the return of each successive response to train-of-four stimulation was noted. Increments of relaxant drug (25% of the initial dose) were given when the third response to the train-of-four stimulation was detectable, or sooner if clinically indicated. On completion of the surgery, anaesthesia was maintained until the train-of-four stimulation produced at least one twitch response. Thereafter, neostigmine 0.02 mg kg$^{-1}$ with atropine was administered; if required, further increments of neostigmine 0.004 mg kg$^{-1}$ were given at 2-min intervals (with additional atropine) until the fourth response to train-of-four stimulation was judged to be essentially of the same magnitude as that of the first response. This was taken as being equivalent to a train-of-four ratio (fourth twitch expressed as a percentage of the first) of 75% or better and therefore indicating adequate antagonism of the neuromuscular blockade for clinical purposes (Ali and Katz, 1973). Anaesthesia was then discontinued. As a further assessment, the patient was asked to open his eyes, protrude the tongue, and raise his head off the pillow after recovery of consciousness.

## RESULTS

Table I shows the duration of action of and spontaneous recovery from the initial dose of Org NC 45 and pancuronium as judged by the return of the train-of-four response, and the corresponding data for the first incremental dose. Two patients were excluded from the Org NC 45 group and three from the pancuronium group; following the intubating dose of relaxant, a diminished first twitch response persisted and thus it was impossible to record the time interval from injection to the re-appearance of the first twitch. This marked variation in response to the relaxants is well recognized.

With the intubating dose (table I), the mean time from injection of Org NC 45 until re-appearance of the first twitch response was 23.5 ± 1.1 min, whereas with pancuronium the corresponding time was 50.5 ± 3.6 min. Thereafter recovery to the third response required a further 8.9 and 23.5 min for Org NC 45 and pancuronium respectively. Similarly, the mean time for recovery from the first incremental dose to the re-appearance of the first response to the train-of-four (table I) was 11.6 ± 0.8 min with Org NC 45 and 31 ± 4.4 min with pancuronium, following which a further 8.7 and 18.3 min respectively were required to achieve a third train-of-four response. It is generally accepted that, in an "adequately" anaesthetized patient, satisfactory muscle relaxation for abdominal surgery exists when two of the train-of-four responses are eliminated (Miller, 1981). These recovery times indicate that Org NC 45 has a significantly shorter duration of action than that of pancuronium ($P < 0.01$).

In figure 1 the return of the train-of-four responses following intubation, and first incremental

TABLE I. *Mean time interval between the re-appearance of each successive twitch of the train-of-four following intubation doses and incremental doses of Org NC 45 and pancuronium. Student's* t *test has been applied and Org NC 45 is shown to be significantly shorter acting than pancuronium (P < 0.01)*

| Time interval between re-appearance of successive twitches of train-of-four | Mean SEM | *n* | Mean SEM | *n* | *P* |
|---|---|---|---|---|---|
|  | Org NC 45 |  | Pancuronium |  |  |
| Intubation dose | 0.1 mg kg$^{-1}$ |  | 0.1 mg kg$^{-1}$ |  |  |
| Injection to 1st twitch (min) | 23.5 ± 1.1 | 23 | 50.5 ± 3.6 | 22 | < 0.01 |
| 1st to 2nd twitch (min) | 5.2 ± 0.7 | 23 | 15.0 ± 2.3 | 12 | < 0.01 |
| 2nd to 3rd twitch (min) | 3.7 ± 0.6 | 7 | 8.5 ± 2.5 | 2 | < 0.01 |
|  | Org NC 45 |  | Pancuronium |  |  |
| First incremental dose | 0.025 mg kg$^{-1}$ |  | 0.025 mg kg$^{-1}$ |  |  |
| Injection to 1st twitch (min) | 11.6 ± 0.8 | 16 | 31.0 ± 4.4 | 7 | < 0.01 |
| 1st to 2nd twitch (min) | 5.1 ± 0.7 | 16 | 10.8 ± 1.6 | 5 | < 0.01 |
| 2nd to 3rd twitch (min) | 3.6 ± 0.4 | 13 | 7.5 ± 1.0 | 4 | < 0.01 |

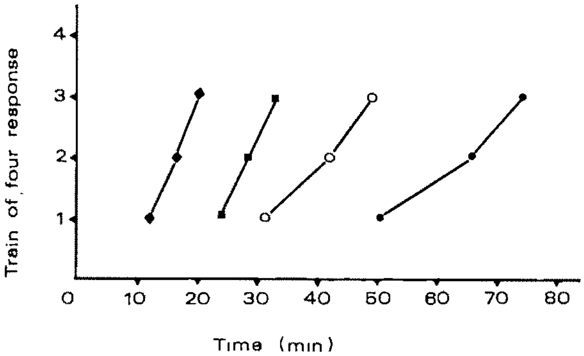

FIG. 1. Recovery of train-of-four response following the intubation doses and first incremental doses of Org NC45 and pancuronium. Each value represents the mean of the time intervals between the re-appearance of successive twitches of the train-of-four. ■ = Org NC45, intubation dose (0.1 mg kg$^{-1}$); ● = pancuronium, intubation dose (0.1 mg kg$^{-1}$); ◆ = Org NC45, first incremental dose (0.025 mg kg$^{-1}$); ○ = pancuronium, first incremental dose (0.025 mg kg$^{-1}$).

doses of both Org NC45 and pancuronium, are plotted against the mean time (min). The steeper slope of the lines joining the points for Org NC45 compared with those for pancuronium reflects the more rapid rate of recovery from the former drug.

Although limitation of operating time precluded the administration of multiple incremental doses to patients in the pancuronium group, the significantly shorter duration of action of Org NC45 frequently allowed several doses to be given within the operating time. Table II shows the data for these patients who received multiple doses of Org NC45.

Satisfactory spontaneous recovery from the blockade produced by Org NC45 (train-of-four ratio greater than 75%) occurred in four patients: in the first patient, 50 min after the initial dose, and in the remaining three, in times ranging from 31 to 40 min following incremental doses (table II).

When the return of the train-of-four response following the initial and each subsequent incremental dose is plotted against time (min) (fig. 2), it can

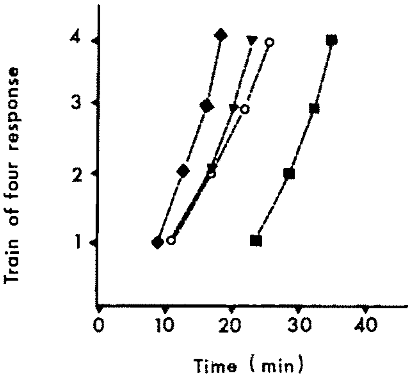

FIG. 2. Recovery of train-of-four response following repeated doses of Org NC45. Each value represents the mean of the time intervals between the re-appearance of successive twitches of the train-of-four. ■ = intubation dose (0.1 mg kg$^{-1}$); ▼ = second dose (0.025 mg kg$^{-1}$); ○ = third dose (0.025 mg kg$^{-1}$); ◆ = fourth dose (0.025 mg kg$^{-1}$).

TABLE II. *Mean time interval between the re-appearance of each successive twitch of the train-of-four following intubation doses and repeated doses of Org NC45. Four patients attained complete neuromuscular recovery without neostigmine*

| Time interval between re-appearance of successive twitches of train-of-four | 1st dose (0.1 mg kg$^{-1}$) | | 2nd dose (0.025 mg kg$^{-1}$) | | 3rd dose (0.025 mg kg$^{-1}$) | | 4th dose (0.025 mg kg$^{-1}$) | |
|---|---|---|---|---|---|---|---|---|
| | Mean SEM | *n* | Mean SEM | *n* | Mean SEM | *n* | Mean SEM | *n* |
| Injection to 1st twitch (min) | 23.5±1.1 | 23 | 11.6±0.8 | 16 | 10.9±1.3 | 7 | 8.8±1.4 | 5 |
| 1st to 2nd twitch (min) | 5.2±0.7 | 23 | 5.1±0.7 | 16 | 5.9±1.3 | 6 | 3.6±0.6 | 5 |
| 2nd to 3rd twitch (min) | 3.7±0.6 | 7 | 3.6±0.4 | 13 | 5.0±1.0 | 4 | 3.0±0.5 | 5 |
| 3rd to 4th twitch (min) | 2.6±0.4 | 5 | 2.6±1.3 | 10 | 3.7±0.4 | 4 | 2.6±0.6 | 5 |
| Total time from injection to full recovery (min) (four patients) | 50 | 1 | 33 | 1 | 40 | 1 | 31 | 1 |

TABLE III. *Doses of neostigmine (mg kg$^{-1}$) required for complete antagonism of neuromuscular blockade. Four Org NC 45 patients did not require neostigmine and are excluded from the overall comparison. Student's* t *test has been applied*

| Train-of-four response at time of neostigmine injection | Neostigmine requirement (mg kg$^{-1}$) | | | | |
|---|---|---|---|---|---|
| | Org NC 45 group | | Pancuronium group | | |
| | Mean SEM | *n* | Mean SEM | *n* | *P* |
| 1 twitch present | 0.030 | 1 | 0.035±0.003 | 12 | >0.05 |
| 2 twitches present | 0.022±0.002 | 6 | 0.030±0.004 | 7 | >0.05 |
| 3 twitches present | 0.020±0.001 | 10 | 0.022±0.001 | 3 | >0.05 |
| 4 twitches present | 0.020±0 | 4 | 0.025±0.002 | 3 | >0.05 |
| Overall | 0.021±0.001 | 21 | 0.031±0.002 | 25 | <0.05 |

be seen that for each dose the recovery rate, as represented by the slope, is similar; each incremental dose completely abolished the train-of-four response for approximately 9–11 min. These results suggest absence of drug cumulation.

The mean total dose of neostigmine required to achieve satisfactory reversal of blockade (train-of-four ratio greater than 75%) in the two groups of patients was compared (table III), the four patients in the Org NC45 group who did not require anticholinesterase having been excluded. Overall, the Org NC 45 group required significantly less neostigmine ($P<0.05$) than those in the pancuronium group. When the two groups were matched for degree of residual neuromuscular block at the time of administration of the antagonist, however, the neostigmine requirement was less in the Org NC 45 group than in the pancuronium group, but the difference was not statistically significant.

The mean onset time as measured from injection until there was no response evoked by the train-of-four stimulation (table IV) was 2.81±0.5 min and 3.47±1.6 min for Org NC 45 and pancuronium respectively. These results are not statistically different. As in table I, the five patients in whom blockade was incomplete were excluded.

TABLE IV. *Time (min) from injection of intubation dose of Org NC 45 and pancuronium to complete abolition of the train-of-four response. (Student's* t *test applied; difference is not significant). Five patients were excluded because of incomplete blockade (see text)*

| | Mean | SD | *n* | *P* |
|---|---|---|---|---|
| Org NC45 | 2.81 | ±0.5 | 23 | >0.05 |
| Pancuronium | 3.47 | ±1.6 | 22 | |

Figures 3 and 4 display the heart rate and arterial systolic pressure changes for the first 30 min following injection of the intubating dose of each drug. Fifteen minutes after injection of the relaxant, when the effects of endotracheal intubation could probably be discounted, the mean heart rate in those patients who had received Org NC 45 was approximately 30 beat min$^{-1}$ less than in those receiving pancuronium. At this time surgery was either about to commence or had merely reached the stage of skin incision. In contrast, the corresponding arterial systolic pressure recordings were not markedly differ-

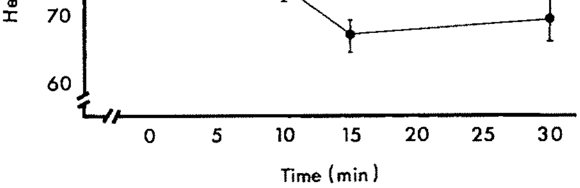

FIG. 3. Changes in heart rate from pre-induction values following injection of intubation doses (0.1 mg kg$^{-1}$) of Org NC45 and pancuronium. The values are expressed as mean ± SEM ($n = 25$ for each group). The heart rate is significantly less in the Org NC45 group from 5 min onwards ($P<0.01$).

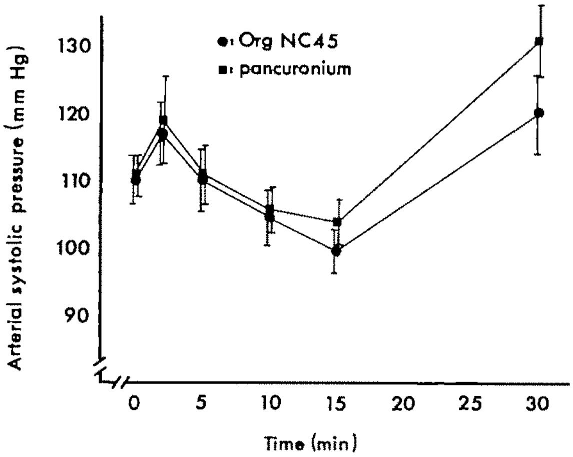

FIG. 4. Changes in arterial systolic pressure from pre-induction values following injection of intubation doses (0.1 mg kg$^{-1}$) of Org NC45 and pancuronium. The values are expressed as mean ± SEM ($n = 25$ for each group). At no time was there a significant difference between the groups.

ent, those in the pancuronium group being only slightly greater than those in the group receiving Org NC45.

## DISCUSSION

There is a need for caution when interpreting the data from a clinical study which does not include large numbers of patients. Nonetheless, our results confirm that, with an anaesthetic technique that excludes volatile agents, Org NC45 has a duration of action between one-third and one-half that of pancuronium. The doses used in this study were recognized as being only approximately equipotent since most previous authors had found Org NC 45 to be a little more potent than pancuronium (Baird and Herd, 1980; Krieg, Crul and Booij, 1980; Viby-Mogensen, Jorgensen et al., 1980; Fahey et al., 1981). Consideration of this fact would probably further emphasize the difference in duration of action between the two drugs.

The relative lack of cumulation following repeated doses of Org NC45 has already been described. In this study patients who received several supplementary doses of Org NC45 showed no evidence of prolonged block.

Recently Gencarelli and Miller (1982), using an elegant technique which took account of the different spontaneous recovery rates of Org NC45 and pancuronium, have shown that, in man, the two drugs are effectively and equally antagonized by neostigmine. In our study those who had received Org NC45 required less neostigmine than those in the pancuronium group for recovery from an equivalent neuromuscular block, although the difference was not statistically significant. This difference could be attributed to a more rapid spontaneous recovery from Org NC45 blockade.

The four patients in whom adequate recovery from Org NC45 blockade was achieved without anticholinesterase are of particular interest. It would seem that, after Org NC 45, provided neuromuscular transmission is monitored, neostigmine may be safely omitted and yet satisfactory recovery be obtained without undue delay. This advantage of Org NC45 was noted by Baird, Bowman and Kerr (1982) with reference to the complications ascribed to neostigmine following ileo-rectal anastomosis (Bell and Lewis, 1968; Wilkins et al., 1970).

In this study the onset time to total block of the evoked response to train-of-four stimulation was slightly shorter with Org NC 45 compared with pancuronium, but the difference was not statistically significant. This finding is in agreement with that of Fahey and colleagues (1981), while Crul and Booij (1980) found Org NC45 to be shorter in onset "but not dramatically so", and Agoston and others (1980), when using the same dose (0.1 mg kg$^{-1}$), described the onset time of both drugs as equal. The relationship between onset time and intubating conditions is complex, however, and the extent of central depression of reflex activity plays an important role. Agoston and others (1980) emphasized that tracheal intubation can be effected with Org NC45 well before there is total block of the evoked response of the adductor pollicis and Norman, Read and Du Boulay (1980) noted that, with this drug, apnoea preceded paralysis of the hand muscles. When comparing Org NC45 0.1 mg kg$^{-1}$ with pancuronium 0.1 mg kg$^{-1}$, Harrison and Feldman (1981) described the intubating conditions at 90 s as being not markedly different and our experience in this study would support this.

At 15 min following injection of Org NC45, and when the surgical stimulus was absent or minimal, there was no evidence of tachycardia; this agrees with the findings from other clinical studies of this drug. Animal experiments have shown that, in contrast to pancuronium and other non-depolarizing agents, Org NC45, in doses 20 times greater than those required for neuromuscular blockade, has no effect on the heart rate, arterial pressure or the sympathetic nervous system (Marshall et al., 1980).

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REFERENCES

Agoston, S., Salt., P., Newton, D., Bencini, A., Boomsma, P., and Erdman, W. (1980). The neuromuscular blocking action of Org NC 45—a new pancuronium derivative in anaesthetized patients. *Br. J. Anaesth.*, 52, 53S.

Ali, H. H., and Kitz, R. J. (1973). Evaluation of recovery from non-depolarizing neuromuscular block, using a digital neuromuscular transmission analyzer. *Anesth. Analg.* (*Cleve.*), 52, 740.

—— Utting, J. E., and Gray, T. C. (1971). Quantitative assessment of residual antidepolarizing block (Part II). *Br. J. Anaesth.*, 43, 478.

Baird, W. L. M., Bowman, W. C., and Kerr, W. J. (1982). Some actions of Org NC 45 and of edrophonium in the anaesthetized cat and in man. *Br. J. Anaesth.*, 54, 375.

—— Herd, D. (1980). A new neuromuscular blocking drug, Org NC 45. *Br. J. Anaesth.*, 52, 61S.

Bell, C. M. A., and Lewis, C. B. (1968). Effect of neostigmine on the integrity of ileo-rectal anastamoses. *Br. Med. J.*, 3, 587.

Bowman, W. C., and Norman, J. (eds), (1980). Symposium on Org NC 45. *Br. J. Anaesth.*, 52, (Suppl. 1).

Crul, J. F., and Booij, L. H. D. J. (1980). First clinical experiences with Org NC 45. *Br. J. Anaesth.*, 52, 49S.

Durant, N. N., Houwertjes, M. C., and Crul, J. F. (1980). Comparison of the neuromuscular blocking properties of Org NC 45 and pancuronium in the rat, cat and rhesus monkey. *Br. J. Anaesth.*, 52, 723.

—— Marshall, I. G., Savage, D. S., Nelson, D. J., Sleigh, T., and Carlyle, I. C. (1979). The neuromuscular and autonomic blocking activities of pancuronium, Org NC 45, and other pancuronium analogues in the cat. *J. Pharm. Pharmacol.*, 31, 831.

Fahey, M. R., Morris, R. B., Miller, R. D., Yung, J. S., Cronnelly, R., and Gencarelli, P. (1981). Clinical pharmacology of Org NC 45 (Norcuron T.M.). *Anesthesiology*, 55, 6.

Gencarelli, P. J., and Miller, R. D. (1982). Antagonism of Org NC 45 (Vecuronium) and pancuronium neuromuscular blockade by neostigmine. *Br. J. Anaesth.*, 54, 53.

Harrison, P., and Feldman, S. A. (1981). Intubating conditions with Org NC 45. *Anaesthesia*, 36, 874.

Kreig, N., Crul, J. F., and Booij, L. H. D. J. (1980). Relative potency of Org NC 45, pancuronium, alcuronium and tubocurarine in anaesthetized man. *Br. J. Anaesth.*, 52, 783.

Marshall, R. J., McGrath, J. C., Miller, R. D., Docherty, J. R., and Lamar, J.-C. (1980). Comparison of the cardiovascular actions of Org NC 45 with those produced by other non-depolarizing neuromuscular blocking agents in experimental animals. *Br. J. Anaesth.*, 52, 21S.

Miller, R. D. (1981). *Anesthesia*, 1st edn., p. 494. New York: Churchill Livingstone.

Norman, J., Read, D., and Du Boulay, M. (1980). Hand and respiratory muscle paralysis produced by Org NC 45 in man. *Br. J. Anaesth.*, 52, 956.

Viby-Mogensen, J., Hansen, P. H., Jorgensen, B. C., Ording, H., Kann, T., and Fries, B. (1980). A new nerve stimulator (Myotest). *Br. J. Anaesth.*, 52, 547.

Viby-Mogensen, J., Jørgensen, B. C., Engbaek, J., and Sørensen, B. (1980). On Org NC 45 and halothane anaesthesia. *Br. J. Anaesth.*, 52, 67S.

Wilkins, J. L., Hardcastle, J. D., Mann, C. V., and Kaufman, L. (1970). Effects of neostigmine and atropine on motor activity of ileum, colon and rectum of anaesthetized subjects. *Br. Med. J.*, 1, 793.

## ETUDES CLINIQUES SUR L'ORG NC 45: COMPARAISON AVEC LE PANCURONIUM

### RESUME

Certaines actions de l'Org NC 45 ont été comparées à celles du pancuronium dans une étude effectuée chez 50 patients anesthésiés au protoxyde d'azote avec des adjuvants morphinomimétiques. La technique du train de quatre a été utilisée pour préciser la récupération du bloc neuromusculaire et son antagonisme. L'Org NC 45 s'est révélé avoir une durée d'action à partir de l'injection d'une dose suffisante pour l'intubation ($0,1\ \mathrm{mg\,kg^{-1}}$) jusqu'à la réapparition de la première réponse du twitch de 23,5 ± 1,1 min; la durée correspondante pour le pavulon $0,1\ \mathrm{mg\,kg^{-1}}$) était de 50,5 ± 3,6 min. Le temps de récupération entre la dose initiale et la réapparation de la première rèponse au train de quatre était 11,6 ± 0,8 min avec l'Org NC 45 et 31 ± 4,7 min avec le pancuronium. Il n'y a pas eu de signes d'accumulation après plusieurs doses croissantes d'Org NC 45. La vitesse d'installation d'une paralysie du muscle adductor pollicis était plus rapide avec l'Org NC 45 qu'avec le pancuronium, mais la différence n'était pas statistiquement significative. Une récupération spontanée satisfaisante du bloc à l'Org NC 45 a pû être obtenue sans délais excessifs. L'Org NC 45 s'est révélé induire une tachycardie significativement moins importante.

## KLINISCHE STUDIEN ÜBER ORG NC 45: VERGLEICH MIT PANCURONIUM

### ZUSAMMENFASSUNG

Einige Wirkungen von Org NC 45 wurden mit denen von Pancuronium in einer Studie an 50 Patienten verglichen. Die Narkose wurde mit Lachgas und weiteren Narkosemitteln durchgeführt. Die train-of-four Technik wurde zur Beurteilung der Erholung der neuromuskulären Blockade und deren Antagonisierung verwendet. Es zeigte sich, daß Org NC 45 eine Wirkungsdauer von der Injektion der Intubationsdosis ($0,1\ \mathrm{mg\,kg^{-1}}$) bis zum Wiederauftreten der ersten Zuck-Antwort von 23,5 ± 1, 1 s besaß. Die entsprechende Zeit für Pancuronium $0,1\ \mathrm{mg\,kg^{-1}}$ betrug 50,5 ± 3,6 min. Die Erholungszeit von der "initial" ansteigenden Dosis bis zum Wiederauftreten der ersten train-of-four Antwort war 11,6 ± 0,8 min bei Org NC 45 und 31 ± 4,7 bei Pancuronium. Es trat keine Akkumulation nach mehreren größer werdenden Dosen von Org NC 45 auf. Die Rate des Einsetzens der Lähmung des M. adductor pollicis war bei Org NC 45 schneller als bei Pancuronium, der Unterschied war aber nicht statistisch signifikant. Ausreichende spontane Erholung von der Org NC 45-Blockade wurde ohne ungewöhnliche Verzögerung erreicht. Org NC 45 verursachte signifikant weniger Tachykardien.

## ESTUDIOS CLÍNICOS DEL ORG NC 45: COMPARACIÓN CON EL PANCURONIO

### SUMARIO

Se llevó a cabo le comparación de algunas acciones del Org NC45 con las del pancuronio en el curso de un estudio de unos 50 pacientes anestesiados con óxido nitroso y complementos narcóticos. Se usó la técnica de la serie-de-cuatro para evaluar la recuperación del bloqueo neuromuscular y su antagonismo. El Org NC45 demostró tener una duración de acción entre la inyección de la dosis de intubación (0,1 mg kg$^{-1}$) y la reaparición de la primera respuesta de contracción, de 23,5 ± 1,1 min.; el periodo correspondiente del pancuronio (0,1 mg kg$^{-1}$) fue de 50,5 ± 3,6 min. El tiempo de recuperación desde la dosis creciente inicial hasta la reaparición de la primera respuesta de serie-de-cuatro fue de 11,6 ± 0,8 min con el Org NC45 y de 31 ± 4,7 min con el pancuronio. No se observó ninguna prueba de acumulación a raíz de las distintas dosis crecientes de Org NC45. El ritmo de acción de la parálisis del abductor del pulgar era mayor con el Org NC45 que con el pancuronio, pero la diferencia no tenía significado desde el punto de vista estadístico. Pudo conseguirse sin demora indebida la recuperación espontánea satisfactoria del bloqueo del Org NC45. Se observó que el Org NC45 produce mucho menos taquicardia.

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# EXTRADURAL AND PARENTERAL MORPHINE: KINETICS AND EFFECTS IN POSTOPERATIVE PAIN. A CONTROLLED CLINICAL STUDY

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A. RANE, B. SCHILDT AND T. SYMRENG

## SUMMARY

In a controlled clinical study of 20 patients undergoing arthrotomy a single dose of morphine 0.05 $\mathrm{mg\,kg^{-1}}$ administered extradurally resulted in more pronounced and prolonged pain relief than morphine 0.1 $\mathrm{mg\,kg^{-1}}$ i.m. in the period immediately after operation. This difference was significant between 2 and 11 h after morphine administration. The maximum analgesic effect for nine patients in the extradural group was obtained about 2 h after injection. Two of 10 in the extradural group experienced urinary retention. Other side-effects were mild for both groups. Plasma concentrations of morphine were measured in five patients in each group. Four hours after administration, morphine was not detectable in plasma in any of the extradural group and in two of the i.m. group. Our study gives further support for the theory that extradural morphine acts on the spinal cord.

The recently developed technique of administering opiates intrathecally and extradurally to relieve pain in man is based on animal studies (Yaksh and Rudy, 1976, 1977) in which small intrathecal doses of opiates in rats were found to produce a dose-dependent increase of the pain threshold. This effect is stereospecific and reversed by naloxone. The analgesia is regional. Low levels of radioactivity are detected in the brain and in the spinal cord distant from the site of injection after intrathecal administration of $^{14}$C-morphine at the lumbar level in rats. Therefore, it was postulated that the analgesic effects of opiates were mediated by a direct action on the substantia gelatinosa. This part of the dorsal horn has a high density of opiate receptors (Atweh and Kuhar, 1976; Snyder, 1977) and is rich in substance P and enkephalin-like material (Hökfelt et al., 1977).

The first clinical report showed that an intrathecal dose of morphine 0.5 or 1.0 mg given to patients with cancer relieved pain for 10–24 h (Wang, Nauss and Thomas, 1979). Several investigators have reported good effects of opiates administered extradurally for postoperative and chronic pain, but not during delivery (Bahar et al., 1979; Torda, 1979; Bromage, Camporesi and Chestnut, 1980; Graham, King and McCaughey, 1980; Husemeyer, O'Connor and Davenport, 1980; Johnston and McCaughey, 1980; Magora et al., 1980; Torda et al., 1980; Reiz et al., 1981).

Most studies show a wide range in duration of analgesia. Morphine 2 mg administered to an unselected group of patients gave pain relief for 6–24 h without any sensory or motor side-effects (Bahar et al., 1979). Good pain relief was achieved for a mean of 16.1 h (SD = 8.1 h) in an uncontrolled study of 21 patients receiving an average of morphine 10 mg extradurally after operation (Bromage, Camporesi and Chestnut, 1980). Variable duration of pain relief after small extradural doses of morphine has been reported by others (Graham, King and McCaughey, 1980; Johnston and McCaughey, 1980; Magora et al., 1980; Reiz et al., 1981).

We are only aware of two strictly controlled studies, both of which were carried out in patients undergoing major gynaecological surgery. McClure and others (1980) found no difference in effect when morphine 2 and 5 mg administered extradurally was compared with saline. Chambers, Sinclair and Scott (1981) reported significantly more prolonged pain relief after extradural compared with i.m. morphine when the drug was administered before surgery. However, they also found that extradural morphine had a slow onset of action when it was administered to patients in pain.

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The purpose of the present investigation was to compare the efficacy of extradural and i.m. morphine since few controlled studies have been published. A further aim was to study the kinetics of morphine after these modes of administration.

## MATERIALS AND METHODS

The study was approved by the local Ethics Committee and was carried out after informed consent from the patients. Twenty healthy male athletes undergoing arthrotomy (table I) (ages 20–41 yr) were treated with diazepam 10 mg rectally 1 h before induction of anaesthesia. No opiates were given before or during the operation. Anaesthesia and surgery were carried out by members of our senior staff.

After surgery, the patients were observed for a minimum of 20 h in the recovery room. They were randomly allocated to two groups when pain relief by opiates was required and when the patients had recovery of motor function of their hips and knees. Preservative-free morphine-HCl and saline in identical bottles were obtained from the hospital pharmacy and given extradurally or i.m. in a double-blind fashion.

Ten patients received morphine-HCl in saline i.m. (0.1 mg kg$^{-1}$ in 0.1 ml saline per kg). These patients also received 0.1 ml of saline per kg extradurally. The other 10 patients recevied morphine-HCl extradurally (0.05 mg kg$^{-1}$ in saline 0.1 ml kg$^{-1}$) and saline 0.1 ml kg$^{-1}$ i.m. Two millilitre of saline was injected after treatment to flush the catheter.

Pain relief was evaluated with the visual analogue scale (VAS) before and 10, 20, 30 min and 1, 2, 3, 5, 7, 11, 15 and 20 h after administration of morphine (Joyce et al., 1975). Trained nurses presented a 100 mm horizontal scale to the patients. A new sheet of paper was used at each evaluation. The patients were asked to mark the distance on the scale that corresponded to the intensity of their pain. Patients received supplementary doses of pethidine-HCl 1.0 mg kg$^{-1}$ i.m. if the effect of morphine failed. The first injection was not given earlier than 30 min after the administration of morphine and was repeated as required. No other drugs were administered during the peri- and postoperative periods.

After the administration of morphine, the systolic and the diastolic arterial pressures and the heart and respiratory rates were monitored for 20 h by trained nurses. The patients were observed for side-effects and the gross motor function of the legs was monitored.

### *Sampling and analyses*

Ten millilitre of blood for measurement of plasma concentrations of morphine was drawn into heparinized plastic tubes from an indwelling venous catheter before administration of morphine and 10, 20 and 30 min and 1, 2, 4, 5, 7 and 19 h after the injection. After centrifugation within 1 h, the plasma was transferred to plastic tubes and frozen at −20 °C. The concentration of morphine was analysed in duplicate within 6 months by mass fragmentography (M. Garle, in preparation). An LKB 2091 Gas Chromatograph–Mass Spectrometer (GCMS) equipped with a multiple ion detector and a GC with a 3% SE-30 column (1.5 m × 2 mm i.d.) was used. The working conditions were: column temperature 230 °C, electron voltage 20 eV. The ions with mass numbers m/e 414 and 418 for morphine and the internal standard, respectively, were monitored. The retention time was 2.5 min for both.

Ammonium-buffer (pH 9.5, 0.1 ml), and 0.1 ml of internal standard (morphine-$^{13}$CD$_3$) were added to 0.8 ml of plasma. The extraction was performed with a Clin-Elute column using 6 ml of

TABLE I. *Clinical data for 10 patients given morphine 0.05 mg kg$^{-1}$ extradurally and 10 patients given 0.1 mg kg$^{-1}$ i.m. (mean ± SD)*

| Group | Age (yr) | Weight (kg) | Level of introducing catheter | Length of catheter in extradural space | Dose of mepivacaine (mg) | Tourniquet time (min) | Surgery time (min) |
|---|---|---|---|---|---|---|---|
| Extradural | 28.8<br>±7.0 | 79.5<br>±7.3 | L3–S1 | 2–3 cm | 344<br>±26.3 | 79<br>±32 | 102<br>±39 |
| I.m. | 29.2<br>±7.4 | 79.0<br>±7.4 | L2–S1 | 2–3 cm | 348<br>±36.8 | 85<br>±33 | 118<br>±35 |
| | n.s. | n.s. | | | n.s. | n.s. | n.s. |

diethylether : isopropanol (8 : 1). The organic phase was evaporated in a Buchler Vortex Evaporator. The pentafluoropropionic acid derivative was formed by reacting the residue with pentafluoropropionic acid anhydride 0.2 ml (Produktkontroll AB), 50% in ethylacetate. Quantification was achieved by running a standard curve in the range 5–100 ng $ml^{-1}$ of plasma and measuring the peak height ratio between morphine and the internal standard. At 19 ng $ml^{-1}$ and 5 ng $ml^{-1}$, the coefficients of variation were 4.8% ($n = 6$) and 5.3% ($n = 6$), respectively. The limit of detection of this method is 1 ng $ml^{-1}$. No interference with the metabolites of morphine or with the other drugs used in the study occurred during the analyses.

### *Statistical evaluation*

The clinical and pharmacokinetic data are presented as means with standard deviation (SD) and the VAS scores are given as means. Significant differences between means were tested by the two-tailed *t* test since it is approximately valid even with quite marked departures from normality (Armitage, 1971). Where parametric assumptions were not met, such as in the comparison of pethidine supplementation, the Mann–Whitney *U* test was used.

Per cent pain relief was calculated for the initial 7 h for nine of 10 extradural patients to determine the pattern of onset of analgesia.

$$\text{Pain relief (\%)} = \frac{\text{pain score before morphine} - \text{pain score after morphine}}{\text{pain score before morphine}} \times 100$$

Plasma concentrations of morphine were analysed in five patients from each group. The peak concentration (ng $ml^{-1}$), time to achieve this (min) and the ratio between peak concentration and dose of morphine per kg body weight (ng $ml^{-1}$/mg $kg^{-1}$) were calculated.

## RESULTS

### *Pain relief*

Small mean pain scores were observed for both groups from 2 to 15 h after administration of morphine (fig. 1). For the period 2–11 h the scores were significantly less in the extradural group in spite of frequent administration of pethidine to the i.m.

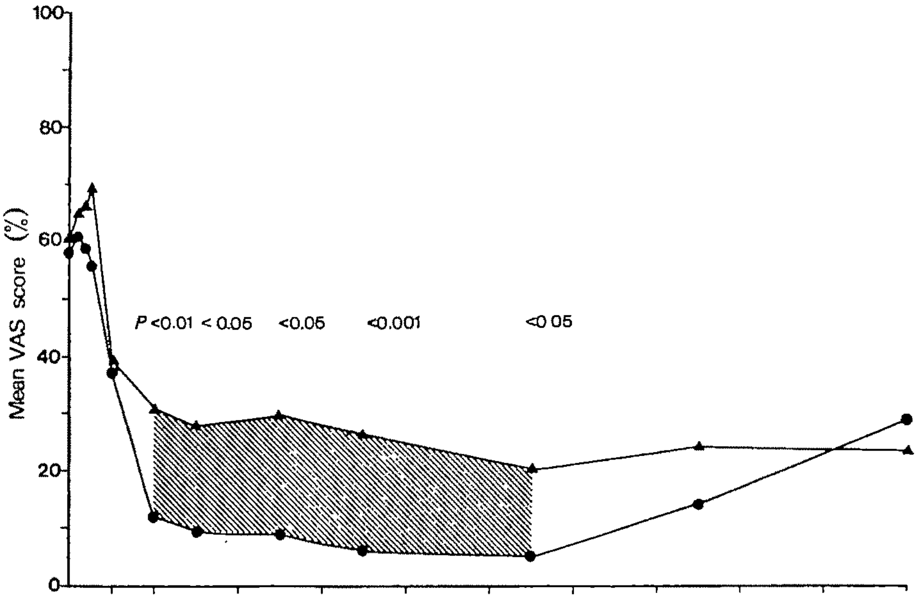

FIG. 1. Mean pain scores (%) for the extradural (●; $n = 10$) and i.m. group (▲; $n = 10$) 0–20 h after administration of morphine (pain score of 100% equivalent to intractable pain). Significant differences are marked by shaded area. The effectiveness of i.m. morphine is over estimated since frequent injections of i.m. pethidine were required.

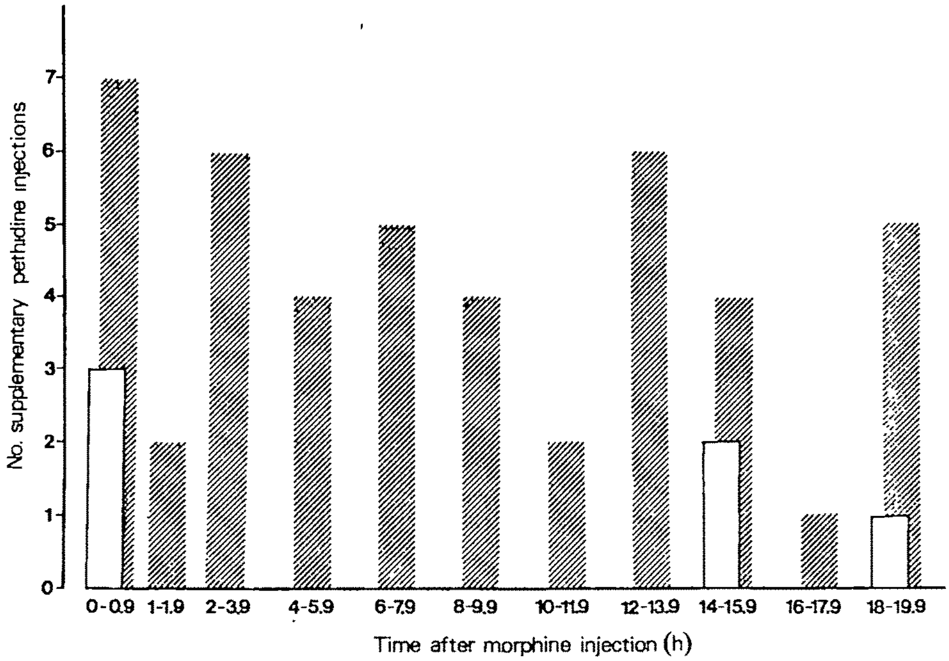

FIG. 2. Number of supplementary injections of pethidine during 20 h after operation for the i.m. (hatched bar) and extradural group (unfilled bar) ($P < 0.001$ for the number of injections during 20 h).

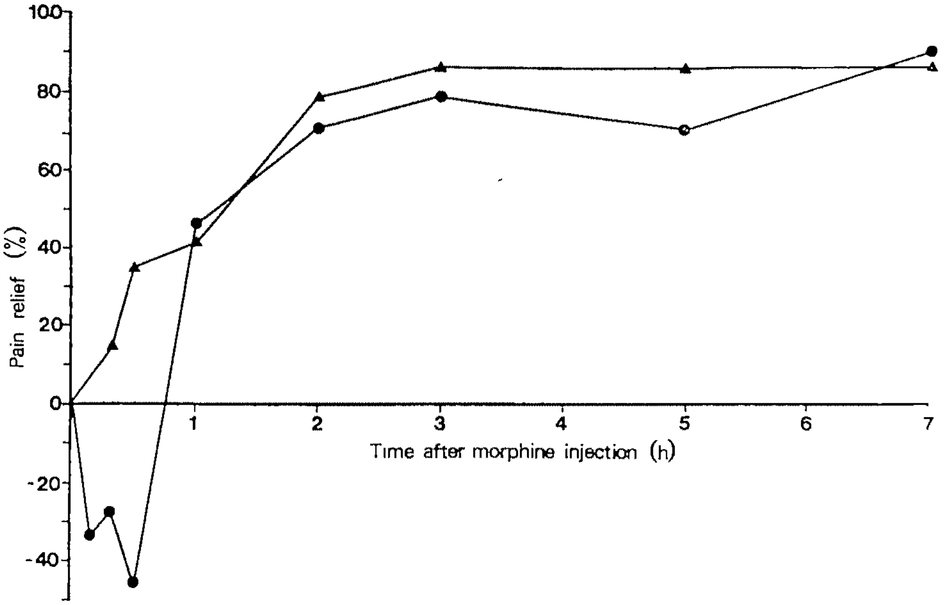

FIG. 3. Pain-relief (%) in nine patients given extradural morphine (negative values indicate increase of pain). The mean of six patients with no pethidine supplementation during the initial hour (▲) and the mean of three with supplementation (●).

group of patients (fig. 2). Mean scores for both of the dose groups did not decrease until 30 min after administration of morphine.

Figure 3 shows that maximum pain relief for nine extradural patients was not achieved until about 2 h after administration of extradural morphine. After the onset of analgesia, the extradural group consistently reported low pain scores, but patients in the i.m. group had a more variable pain relief (figs 1 and 4).

The need for supplementary pethidine injections differed significantly between the groups ($P < 0.001$; fig. 2). The median number of supplementary injections was 0 and 5 for the extradural and i.m. groups, respectively. The total dose of pethidine during 20 h ranged from 1 to 10 mg $kg^{-1}$ in the i.m. group. The requirements for supplementary injections was evenly spread over 20 h. In the extradural group, only three patients required pethidine during the first 15.5 h and these injections were given during the first hour after operation.

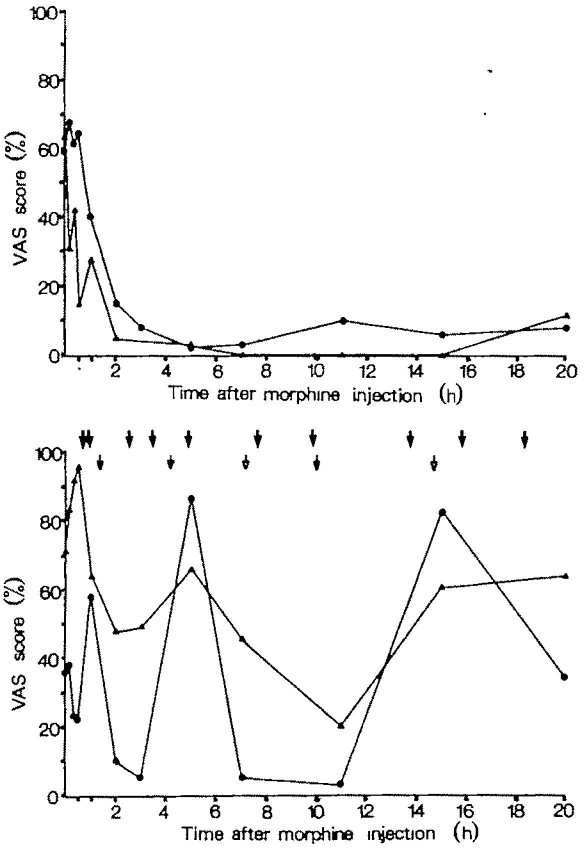

FIG. 4. Individual pain scores (%) during 20 h after operation for two patients (No. 2 = ●, No. 7 = ▲) from the i.m. group (lower panel) and for two patients (No. 2 = ●; No. 7 = ▲) from the extradural group (upper panel). Arrows indicate times of injection of pethidine (patient 2 = open arrows, patient 7 = solid arrows).

All patients in the extradural group could mobilize their knee-joint 2–3 h after operation, but this was not possible for any patient in the i.m. group. No depression in the motor function of the legs was noticed in any patient of either group.

### *Side-effects*

Two patients in the extradural group had urinary retention that required catheterization. Two patients in each group experienced nausea with or without vomiting. No itching or decrease in arterial pressure was observed in any patient.

The respiratory rate was normal in both groups during the 20 h after operation. One hour after administration of morphine mean $Pa_{O_2}$ was 11.5 (SD = 0.8) and 11.7 (SD = 1.1) kPa for the extradural and i.m. groups respectively. The corresponding values for $Pa_{CO_2}$ were 5.3 (SD = 0.4) and 5.3 (SD = 0.3).

### *Pharmacokinetics*

The pharmacokinetic data for morphine after extradural and i.m. administration are given in table II. Figure 5 shows that small concentrations of morphine are detectable in plasma 3–4 h or later after both modes of administration.

## DISCUSSION

This investigation shows that extradural administration results in more pronounced and prolonged pain relief than i.m. morphine even when the i.m. dose is twice as great. After the initial hour, none of the patients in the extradural group required any supplementary pethidine injections for 14.5 h, in contrast to all patients in the i.m. group. To our knowledge, this is the first controlled clinical study which demonstrates that extradural morphine is effective in treating pain after arthrotomy. A case report appeared recently in which a long-lasting analgesic effect of extradural morphine after arthrotomy was described (Ebert and Varner, 1980).

We did not observe the pronounced variability in duration of analgesia after extradural morphine that has been reported previously (Bahar et al., 1979; Bromage, Camporesi and Chestnut, 1980; Johnston

TABLE II. *Pharmacokinetic data of morphine after extradural* (n = *5, 0.05 mg kg*$^{-1}$) *and i.m. administration* (n = *5, 0.1 mg kg*$^{-1}$). $^*C_{max}$ = *peak plasma concentration*

| Patient | Dose (mg) | $C_{max}$* (ng ml$^{-1}$) | Time to $C_{max}$ (min) | $C_{max}$/dose ratio |
|---|---|---|---|---|
| Extradural group | | | | |
| 1 | 4.75 | 18.5 | 10 | 415.7 |
| 2 | 3.75 | 18.3 | 11 | 411.2 |
| 4 | 4.00 | 13.2 | 20 | 298.9 |
| 5 | 3.75 | 28.0 | 10 | 629.2 |
| 6 | 4.25 | 19.0 | 11 | 427.0 |
| Mean ± SD | 4.10 ± 0.42 | 19.4 ± 5.4 | 12.4 ± 4.4 | 436.4 ± 119.6 |
| I.m. group | | | | |
| 2 | 8.5 | 28.0 | 20 | 314.6 |
| 5 | 8.0 | 26.6 | 10 | 298.9 |
| 6 | 7.5 | 31.9 | 30 | 358.4 |
| 8 | 8.5 | 18.4 | 60 | 206.7 |
| 9 | 8.5 | 20.4 | 30 | 229.2 |
| Mean ± SD | 8.20 ± 0.44 | 25.1 ± 5.6 | 30 ± 18.7 | 281.6 ± 144.8 |

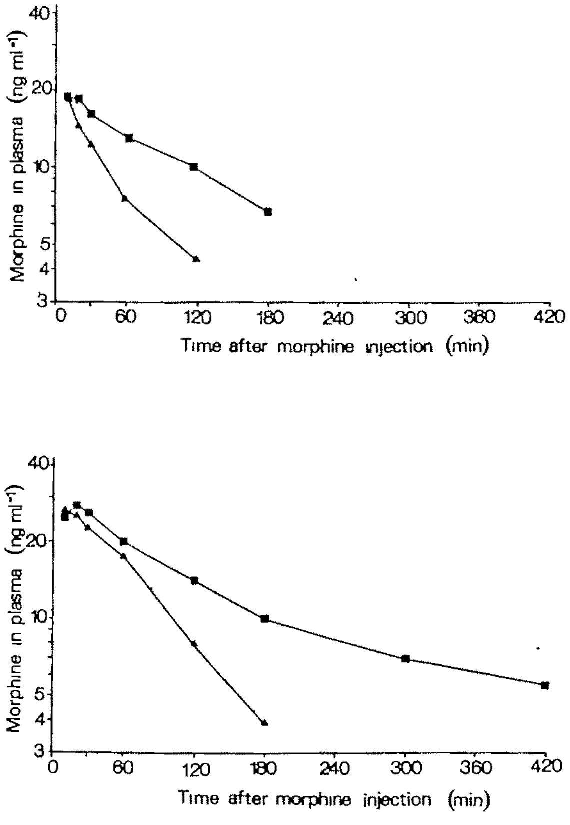

FIG. 5. Two plasma concentration plots from patients in the i.m. (lower panel; ■ = patient No. 2; ▲ = patient No. 5) and extradural group (upper panel; ■ = patient No. 1; ▲ = patient No. 2).

and McCaughey, 1980; Magora et al., 1980; Torda et al., 1980). Variability is likely to occur if the patient groups are not matched for age and operations.

In most of our patients, the full effect of extradural morphine was not achieved until 2 h after injection (fig. 3). This latent period is longer than the 5–10 min reported by Bahar and others (1979). However, a long latency has been observed by some investigators after extradural compared with i.m. morphine (Bromage, Camporesi and Chestnut, 1980; Chambers, Sinclair and Scott, 1981; Reiz et al., 1981). In fact Chambers found that extradural morphine frequently failed to relieve pain in patients because of the prolonged onset of effect. The long latency may be explained by the low lipid solubility of morphine resulting in slow passage across the dura and the dorsal part of the spinal cord (Yaksh, 1981).

Although some criticism has been made of VAS (Maxwell, 1978), this scale has been useful in studies of the effects of extradural and intrathecal morphine (Bahar et al., 1979; McClure et al., 1980) and for monitoring postoperative pain (Chakravarty et al., 1979). VAS was more satisfactory for assessing chronic pain than a fixed interval scale (Joyce et al., 1975). Reproducible VAS scores have been obtained after repeated pain assessment with the VAS test in patients treated with pethidine 140 mg i.m. (Revill et al., 1976).

The mean peak plasma concentration of morphine was 29% greater after i.m. than after extradural administration. However, when correction was made for differences in dose per kg body weight, the extradural group had 55% greater mean concentration:dose ratio (peak plasma concentration/dose per kg body weight) than the i.m. group. This unexpected difference may be related to slow absorption from the i.m. site of injection in the period after operation. Indirect support for this assumption is provided by data from Stanski, Greenblatt and Lowenstein (1978). In their study, the corresponding values after i.m. administration of morphine to healthy volunteers were twice as great as in our patients who received morphine i.m. The reason for the small concentration:dose ratios in our patients is unclear. It is unlikely that previous anaesthesia with mepivacaine has impaired the absorption of i.m. morphine, since this type of anaesthesia increases blood flow in the legs (Modig, Malmberg and Karlström, 1980).

We did not notice late respiratory depression as previously reported for single cases (Boas, 1980; Reiz and Westberg, 1980; Gustafsson, Feychting and Klingstedt, 1981) and the two groups did not differ in respiratory function during the first 20 h. Urinary retention was observed in two patients in the extradural group. Two persons in each group experienced nausea with or without vomiting. These side eside effects have also been observed in a study with a larger patient population (Reiz and Westberg, 1980).

The dissociation between plasma concentrations and pain relief (negligible morphine in plasma of patients in the extradural group after 4 h despite continued pain relief) supports the hypothesis that the pain-relieving effect may be mediated by a direct spinal action of morphine (Yaksh and Rudy, 1976; 1979). It cannot be excluded that morphine in some way induces analgesia after inhibiting release of substance P. This is consistent with the observation of a decreased release of substance P from the spinal cord in animals after intrathecal administration of morphine (Yaksh et al., 1980). The possibility of such an action in man is supported by the observation of a decrease of substance P concentration in lumbar cerebrospinal fluid (c.s.f.) in patients with high c.s.f. concentrations of pethidine after i.v. self-administration (Tamsen, 1981).

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## REFERENCES

Armitage, P. (1971). *Statistical Methods in Medical Research*, p. 106. Edinburgh, Oxford: Blackwell Scientific Publications.

Atweh, S. F., and Kuhar, M. J. (1976). Autoradiographic localization of opiate receptors in rat brain. I: Spinal cord and lower medulla. *Brain Res.*, **124**, 53.

Bahar, M., Magora, F., Olshwang, D., and Davidson, J. T. (1979). Epidural morphine in treatment of pain. *Lancet*, **2**, 527.

Bromage, P. R., Camporesi, E., and Chestnut, D. (1980). Epidural narcotics for postoperative analgesia. *Anesth. Analg. (Cleve.)*, **59**, 473.

Boas, R. A. (1980). Hazards of epidural morphine. *Anaesth. Intens. Care*, **8**, 377.

Chakravarty, K., Tucker, W., Rosen, M., and Vickers, M. D. (1979). Comparison of buprenorphine and pethidine given intravenously on demand to relieve postoperative pain. *Br. Med. J.*, **2**, 895.

Chambers, W. A., Sinclair, C. J., and Scott, D. B. (1981). Extradural morphine for pain after surgery. *Br. J. Anaesth.*, **53**, 921.

Ebert, J., and Varner, P. D. (1980). The effective use of epidural morphine sulphate for postoperative orthopedic pain. *Anesthesiology*, **53**, 257.

Graham, S. L., King, R., and McCaughey, W. (1980). Postoperative pain relief using epidural morphine. *Anaesthesia*, **35**, 158.

Gustafsson, L. L., Feychting, B., and Klingstedt, C. (1981). Late respiratory depression after concomitant use of morphine epidurally and parenterally. *Lancet*, **1**, 892.

Husemeyer, R. P., O'Connor, M. C., and Davenport, H. T. (1980). Failure of epidural morphine to relieve pain in labour. *Anaesthesia*, **35**, 161.

Hökfelt, T., Ljungdahl, Å., Terenius, L., Elde, R., and Nilsson, G. (1977). Immunohistochemical analysis of peptide pathways possibly related to pain and analgesia: enkephalin and substance P. *Proc. Natl Acad. Sci.* (U.S.A.), **74**, 3081.

Johnston, S. R., and McCaughey, W. (1980). Epidural morphine for postoperative pain. *Lancet*, **1**, 975.

Joyce, C. R. B., Zutshi, D. W., Hrubes, V., and Mason, R. M. (1975). Comparison of fixed interval and visual analogue scales for rating chronic pain. *Eur. J. Clin. Pharmacol.*, **8**, 415.

McClure, J. H., Chambers, W. A., Moore, E., and Scott, D. B. (1980). Epidural morphine for postoperative pain. *Lancet*, **1**, 975.

Magora, F., Olshwang, D., Eimerl, D., Shorr, J., Katzenelson, R., Cotev, S., and Davidson, J. T. (1980). Observations on extradural morphine analgesia in various pain conditions. *Br. J. Anaesth.*, **52**, 247.

Maxwell, C. (1978). Sensitivity and accuracy of the visual analogue scale: physico–physical classroom experiment. *Br. J. Clin. Pharmacol.*, **6**, 15.

Modig, J., Malmberg, P., and Karlström, G. (1980). Effect of epidural versus general anaesthesia on calf blood flow. *Acta Anaesthesiol. Scand.*, **24**, 305.

Reiz, S., Ahlin, J., Ahrenfeldt, B., Andersson, M., and Andersson, S. (1981). Epidural morphine for postoperative pain relief. *Acta Anaesthesiol. Scand.*, **25**, 111.

Reiz, S., and Westberg, M. (1980). Side-effects of epidural morphine. *Lancet*, **2**, 203.

Revill, S. I., Robinson, J. O., Rosen, M., and Hogg, M. I. J. (1976). The reliability of a linear analogue scale for evaluating pain. *Anaesthesia*, **31**, 1191.

Snyder, S. H. (1977). Opiate receptors in the brain. *N. Engl. J. Med.*, **296**, 266.

Stanski, D. R., Greenblatt, D. S., and Lowenstein, E. (1978). Kinetics of intravenous and intramuscular morphine. *Clin. Pharmacol. Ther.*, **24**, 52.

Tamsen, A. (1981). Patient-controlled analgesic therapy. Medical thesis, Uppsala University, Uppsala, Sweden.

Torda, T. A. (1979). Epidural analgesia with morphine. A preliminary communication. *Anaesth. Intens. Care*, **7**, 367.

—— Pybus, D. A., Liberman, H., Clark, M., and Crawford, M. (1980). Experimental comparison of extradural and i.m. morphine. *Br. J. Anaesth.*, **52**, 939.

Yaksh, T. L. (1981). Spinal opiate analgesia: characteristics and principles of action. *Pain*, **11**, 293.

—— Jessell, T. M., Gamse, R. R., Mudge, A. W., and Leeman, S. E. (1980). Intrathecal morphine inhibits substance P release from mammalian spinal cord *in vivo*. *Nature (Lond.)*, **286**, 155.

—— Rudy, T. A. (1976). Analgesia mediated by a direct spinal action of narcotics. *Science*, **192**, 1357.

—— —— (1977). Studies on the direct spinal action of narcotics in the production of analgesia in the rat. *J. Pharmacol. Exp. Ther.*, **202**, 1357.

Wang, S. K., Nauss, L. A., and Thomas, E. J. (1979). Pain relief by intrathecally applied morphine in man. *Anesthesiology*, **50**, 149.

## MORPHINE PAR VOIE PERIDURALE ET PARENTERALE: CINETIQUE ET EFFETS SUR LA DOULEUR POST-OPERATOIRE. UNE ETUDE CLINIQUE CONTROLEE

### RESUME

Dans une étude clinique contrôlée de 20 patients subissant une arthrotomie, une dose unique de morphine 0,05 mg kg$^{-1}$, administrée par voie péridurale, entraînait une analgésie plus prononcée et prolongée que la morphine 0,1 mg kg$^{-1}$ i.m. dans la période post-opératoire immédiate. Cette différence était significative entre 2 et 11 h après l'administration de morphine. L'effet analgésique maximum, chez neuf patients du groupe "péridurale" était obtenu environ 2 h après l'injection. Deux des dix patients du groupe "péridurale" ont eu une rétention d'urines. Les autres effets secondaires étaient faibles dans les deux groupes. Les concentrations plasmatiques de morphine étaient mesurées chez cinq patients de chaque groupe. Quatre heures après l'administration, la morphine n'était décelable dans le plasma d'aucun patient du groupe "péridurale" ni chez deux patients du groupe i.m. Notre étude apporte des arguments supplémentaires pour dire que la morphine par voie péridurale agit sur la moëlle épinière.

## PERIDURALES UND PARENTERERALES MORPHIUM: KINETIK UND WIRKUNG AUF POSTOPERATIVE SCHMERZEN. EINE KONTROLLIERTE KLINISCHE STUDIE

### ZUSAMMENFASSUNG

In einer kontrollierten klinischen Studie an 20 Patienten, die sich einer Arthrotomie unterziehen mußten, führte eine einzige Dosis von Morphium 0,05 mg kg$^{-1}$ peridural verabreicht zu einer ausgeprägteren und längeren Schmerzerleichterung als Morphium 0,1 mg kg$^{-1}$ i.m. unmittelbar nach der Operation gegeben. Dieser Unterschied war signifikant zwischen 2 und 11 h nach Morphingabe. Die stärkste analgetische Wirkung für neun Patienten in der periduralen Gruppe wurde ungefähr 2 h nach der Injektion erreicht. Zwei von 10 Patienten in der Periduralgruppe litten an Harnretention. Andere Nebenwirkungen waren in beiden Gruppen mild. Die Plasmakonzentrationen von Morphium wurden bei fünf Patienten in jeder Gruppe gemessen. Vier Stunden nach Verabreichung war kein Morphium im Plasma zu finden bei allen aus der periduralen Gruppe und bei zwei aus der i.m.-Gruppe. Unsere Untersuchung untermauert die Theorie, daß peridurales Morphium auf das Rückenmark wirkt.

## ADMINISTRACION DE MORFINA EXTRADURAL E INTRAMUSCULARMENTE: ASPECTOS CINETICOS Y EFECTOS DURANTE EL PERIODO POSOPERATIVO. UN ESTUDIO CLINICO BAJO CONTROL

### SUMARIO

Durante un estudio clínico controlado de 20 pacientes sometidos a artrotomía, una sóla administración extradural de 0,05 mg kg$^{-1}$ de morfina produjo un alivio del dolor que fue más prolongado e intenso que el obtenido con la administración intramuscular de 0,1 mg kg$^{-1}$ de la misma sustancia durante el periodo inmediatamente posterior a la operación. Esta diferencia fue significativa en el periodo comprendido entre 2 y 11 horas después de la administración de la morfina. El efecto analgésico más alto, correspondiente a nueve pacientes del grupo extradural, se obtuvo unas 2 horas después de la inyección. Dos de los 10 en el grupo de administración extradural experimentaron retención de orina. Los efectos secundarios de otro tipo fueron livianos en ambos grupos. Se midieron las concentraciones de morfina en el plasma en cinco pacientes de cada grupo. A las cuatro horas de haberse efectuado la administración ya no se detectó rastro alguno de morfina en el plasma en ninguno de los pacientes del grupo extradural ni del grupo de administración intramuscular. Nuestro estudio aporta más evidencia que soporta la teoría de que la morfina administrada extraduralmente actúa en la espina dorsal.

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# URINARY RETENTION DURING I.M. AND EXTRADURAL MORPHINE ANALGESIA

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## SUMMARY

In the postoperative period fifty-six healthy patients undergoing cholecystectomy or operations for duodenal ulcer, received, in a randomized order, i.m., "high-level" or "low-level" extradural morphine. Thirty-five per cent in the i.m. group, 33% in the high-level group and 50% in the low-level group suffered urinary retention, in all cases within the first 24 h. The mean cumulative dose of morphine necessary for pain relief was in the same range (13.4–16.5 mg) during the first 2 h of therapy for all groups, while the amounts after 24 and 48 h were twice to four times with the i.m. route compared with the extradural route. A peripheral effect of morphine on the urinary bladder is possible and the mechanism of action is discussed.

Several reports have indicated that effective and prolonged pain relief can be obtained in man by the injection of small doses of morphine into the extradural space (Behar et al., 1979; Cousins et al., 1979; Bromage, Camporesi and Chestnut, 1980). Compared with the i.m. administration of morphine, extradural application has a longer duration of action and is associated with fewer side-effects such as nausea and vomiting (Reiz et al., 1981).

However, undesirable side-effects of extradural morphine such as respiratory depression, pruritus and urinary retention have been noted in several studies (Scott and McClure, 1979; Boas, 1980; Hales, 1980; Reiz and Westberg, 1980; Bromage et al., 1981). Although frequencies between 3% (Magora et al., 1980) and 100% (Weddel and Ritter, 1981; Bromage et al., 1981) of acute urinary retention have been shown, little attention has been paid to this effect. Reiz and others (1981), studying a small group of patients, noted urinary retention in 20% and 0% of patients after extradural and i.m. morphine respectively.

The present study compares the frequency of urinary retention during postoperative pain relief with extradural and i.m. morphine with special reference to the influence of high-level and low-level extradural morphine administration.

## PATIENTS AND METHODS

The study was approved by the local ethics committee and informed consent was obtained from all the patients.

Thirty-six patients undergoing cholecystectomy and 20 patients operated upon for a duodenal ulcer were studied. None suffered from cardiopulmonary or other severe systemic diseases.

The patients were premedicated with oral diazepam 10–20 mg according to weight. Anaesthesia was induced with thiomebumal preceded by atropine; suxamethonium was given to facilitate tracheal intubation. Anaesthesia was maintained with nitrous oxide in oxygen, enflurane and pancuronium; opiates were not given. After the operation the neuromuscular block was antagonized with an atropine and neostigmine mixture. At the time of extubation pethidine was given i.v. (maximum $0.5\,mg\,kg^{-1}$).

In patients undergoing cholecystectomy there was a subcostal incision and those with an ulcer had a combined median and subcostal incision.

Before the surgical procedure the patients were randomly allocated to a postoperative regimen with either i.m. morphine in 5–10 mg doses or with extradural morphine in single doses of 4 mg in 10 ml isotonic saline without preservative.

In extradural groups an extradural catheter was inserted either to the vertebral interspace L1–L2 or to L3–L4. In the first group an attempt was made to move the catheter 10 cm cranially. In the second group the catheter was inserted 2–3 cm to the extradural space.

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On the 4th day after operation the height of the catheter tip was tested with 1% lignocaine 5 ml by noting the dermatome level of subjective change in sensation to cold.

During the first 24 h from the start of the operation 2.5–3.0 litre of fluid was given i.v.

Initially extradural morphine was administered at 20-min intervals until complete pain relief at rest was reported. Thereafter, morphine was given only at the request of the patient in a dose sufficient to obtain complete pain relief.

All patients were taken to the same recovery unit for 14–18 h after surgery.

Urinary retention was noted if the patient had the sensation and discomfort of a full bladder or the anaesthetist could palpate a distended bladder. The patient was then encouraged to void during the following hour.

*Statistical methods.* The frequencies of urinary retention in the three groups were compared by a rank sum test.

## RESULTS

Four of 36 patients in the extradural group were excluded from the study (dural puncture, two patients; slip of catheter, one patient; missing test, one patient).

Urinary retention occurred in all three groups of patients, in 33–50% of patients (table I). There was no statistically significance between the three treatments.

Retention occurred 11.4–13.2 h (means) after start of morphine treatment (table I).

Two patients urinated after i.v. administration of naloxone 0.4 mg, two patients urinated after i.m. administration of carbachol 0.125–0.250 mg s.c. The remainder of patients with urinary retention received a bladder catheter.

The cumulative dose of morphine needed during the first 2 h of therapy was similar for the three different routes of administration with mean values ranging from 13.4 to 16.5 mg (table II). After 24 and 48 h the amounts needed in the group of patients treated with i.m. morphine were about two to three times as great as the requirements of patients receiving extradural morphine (table II).

Respiratory depression was not noted in any patient and, except for one case of severe itching, no side-effects were noted.

## DISCUSSION

The use of extradural morphine for pain relief is based on the work of Snyder and Childers (1979), Yaksh and Rudy (1976, 1977), and Yaksh (1978) in animals. They attributed the effect of such treat-

TABLE I. *Clinical data and randomization of 52 patients receiving postoperative analgesic therapy with morphine*

| Treatment group | No. patients F:M | No. patients Total | Age (yr) (mean ± SD) | Urinary retention (No. patients) F:M | Urinary retention (No. patients) Total | Time (h) after start of therapy (mean and range) |
|---|---|---|---|---|---|---|
| I.m | 8:12 | 20 | 48.1 ± 13.0 | 4:3 | 7 (35%) | 11.4 (3–21) |
| Extradural | | | | | | |
| High-level | 8: 4 | 12 | 46.8 ± 15.3 | 2:2 | 4 (33%) | 12.1 (7–19) |
| Low-level | 10:10 | 20 | 40.0 ± 11.9 | 4:6 | 10 (50%) | 13.2 (7–18) |

TABLE II. *Cumulative doses of morphine (mg) (mean ± SD) administered i.m. and extradurally*

| Treatment group | No. patients | Time after start of therapy (h) 0–2 | 0–24 | 0–48 |
|---|---|---|---|---|
| I.m. | 20 | 16.5 ± 3.5 | 59.7 ± 15.6 | 91.9 ± 24.7 |
| Extradural | | | | |
| High-level | 12 | 14.3 ± 3.2 | 25.0 ± 8.0 | 32.3 ± 7.7 |
| Low-level | 20 | 13.4 ± 3.5 | 18.6 ± 5.2 | 25.9 ± 8.0 |

ment to a selective spinal analgesia caused by direct action of the narcotic on spinal opiate receptors that are richly distributed in the posterior horn of the spinal cord. Magora and colleagues (1980) clearly showed that the opiate was present in the cerebrospinal fluid 10–20 min after extradural injection of morphine 2 mg, and that it reaches peak values of 28 ng $ml^{-1}$ after 35 min.

A significant amount of morphine reaches the systemic circulation with an average peak concentration of 49.7 ± 35.6 ng $ml^{-1}$ within 5–30 min after an extradural injection of 10 mg per 70 kg compared with 61.6 ± 31.1 ng $ml^{-1}$ within 15–30 min after a similar dose given i.m. (Weddel and Ritter, 1981). As the frequency of urinary retention seems to be similar after i.m., high-level and low-level morphine injection, the effect on the urinary bladder, if influenced by morphine at all, seems to be peripheral.

The nervous control of the urinary bladder is complex, mediated via both the parasympathetic and the sympathetic nervous system (Nyo, 1969). Sacral parasympathetic nerve fibres via the pelvic nerves mediate detrusor contraction, while sympathetic nerve fibres via the inferior mesenteric plexus and the hypogastric nerves from the 10th thoracic to the 4th sacral sympathetic ganglia (Todd and Mack, 1966) are essential for the sphincter function of the urethra. It is known from *in vitro* studies on isolated strips of detrusor muscles from rabbit and man (S. E. Husted, unpublished observations) that morphine and encephalins serve as potent presynaptic inhibitors of acetylcholine release from postganglionic neurons, an effect completely reversed by naloxone. It is still uncertain if urinary retention during morphine therapy involves an effect on the tone of the internal sphincter (Magora et al., 1980) or on parasympathetic outflow from the sacral cord (Yaksh, 1981), or a local anaesthetic effect on bladder innervation (Boas, 1980). An effect via specific receptors, however, seems plausible as systemic administration of naloxone can antagonize these symptoms (Yagishita et al., 1978; Bromage et al., 1981).

A central effect of morphine on sensation and discomfort of the full bladder may contribute to the occurrence of urinary retention during treatment with morphine.

Symptoms of urinary retention usually occur about 12 h after commencing morphine therapy (Weddel and Ritter, 1981), when relatively large doses may have been given. Bromage, Camporesi and Chestnut (1980) used an initial extradural dose of 10.3 ± 2.5 mg in patients after upper abdominal surgery to obtain complete pain relief.

## REFERENCES

Behar, M., Magora, F., Olshwang, D., and Davidson, J. T. (1979). Epidural morphine in treatment of pain. *Lancet*, 1, 527.

Boas, R. A. (1980). Morpheus without dreams. *Reg. Anesth.*, 5, 2.

Bromage, P. R., Camporesi, E., and Chestnut, D. (1980). Epidural narcotics for postoperative analgesia. *Anesth. Analg. (Cleve.)*, 59, 473.

———— Durant, P. A. C., and Nielsen, C. H. (1981). Rostral spread of epidural morphine. *Anesthesiology*, 55, A149.

Cousins, M. J., Mather, L. E., Glynn, C. J., Wilson, P. R., and Graham, J. R. (1979). Selective spinal analgesia. *Lancet*, 1, 1141.

Hales, P. (1980). Pruritus after epidural morphine. *Lancet*, 1, 204.

Magora, F., Olshwang, D., Eimerl, D., Shorr, J., Katzenelson, R., Cotev, S., and Davidson, J. T. (1980). Observations on extradural morphine analgesia in various pain conditions. *Br. J. Anaesth.*, 52, 247.

Nyo, M. M. (1969). Innervation of the bladder and urethra. *J. Anat.*, 105, 210.

Reiz, S., Ahlin, J., Ahrenfeldt, B., Andersson, M., and Andersson, S. (1981). Epidural morphine for postoperative pain relief. *Acta Anaesthesiol. Scand.*, 25, 111.

—— Westberg, M. (1980). Side-effects of epidural morphine. *Lancet*, 1, 203.

Scott, D. B., and McClure, J. (1979). Selective epidural analgesia. *Lancet*, 1, 1410.

Snyder, S. H., and Childers, S. R. (1979). Opiate receptors and opioid peptides. *Ann. Rev. Neurosci.*, 2, 35.

Todd, J. K., and Mack, A. J. (1966). A study of human bladder detrusor muscle. *Br. J. Urol.*, 41, 448.

Weddel, S. J., and Ritter, R. R. (1981). Serum levels following epidural administration of morphine and correlation with relief of postsurgical pain. *Anesthesiology*, 54, 210.

Yagishita, Y., Fukuda, K., Morioka, T., Karo, T., and Araki, Y. (1978). Intrathecal application of morphine. I. As a supplement action of anesthesia and a prolonged relief of postoperative pain. *Jap. J. Anesth.*, 21, 1584.

Yaksh, T. L. (1978). Analgesic actions of intrathecal opiates in cats and primate. *Brain Res.*, 153, 205.

—— (1981). Spinal opiate analgesia: characteristics and principles of action. *Pain*, 11, 293.

—— Rudy, T. A. (1976). Analgesia mediated by a direct spinal action of narcotics. *Science*, 192, 1352.

———— (1977). Studies on the direct spinal action of narcotics in the production of analgesia in the rat. *J. Pharmacol. Exp. Ther.*, 202, 411.

## RETENTION D'URINES AU COURS D'ANALGESIES A LA MORPHINE I.M. OU PAR VOIE PERIDURALE

### RESUME

Au cours de la période post-opératoire, cinquante-six patients en bonne santé subissant une cholecystectomie ou une intervention

pour ulcère duodénal ont reçu de façon aléatoire de la morphine i.m. par voie péridurale "haute" ou "basse". Trente-cinq pour cent des patientts du groupe i.m., 33% de ceux du groupe péridurale "haute" et 50% du groupe péridurale "basse" ont souffert de rétention d'urines, dans tous les cas au cours des premières 24 h. La dose totale moyenne de morphine, nécessaire pour soulager la douleur, était du même ordre de grandeur (13,4–16,5 mg) pour tous les groupes, au cours des premières 2 h de traitement alors que les quantités étaient de deux à quatre fois plus importantes après 24 et 48 h avec la voie i.m. par rapport à la voie péridurale. Un effet périphérique de la morphine sur la vessie est possible et le mécanisme d'action est discuté.

## URINRETENTION WÄHREND I.M.- UND PERIDURALANALGESIE MIT MORPHIUM

### ZUSAMMENFASSUNG

Postoperativ erhielten sechsundfünfzig gesunde Patienten, die sich einer Cholezystektomie oder einer Operation wegen eines Duodenalulkus unterziehen mußten, nach Randomisierung i.m., und "höher" oder "tiefer" peridural appliziertes Morphium. 35% in der i.m. Gruppe, 33% in der "hohen" und 50% in der "tiefen" Gruppe litten an Urinretention innerhalb der ersten 24 h. Die durchschnittliche (kumulative) Dosis, die zu Schmerzerleichterung notwendig war, bewegte sich in der selben Größenordnung (13,4–16,5 mg) während den 2 ersten Stunden der Therapie bei allen Gruppen, während die Mengen bei der i.m. Anwendung zwei– bis viermal größer waren nach 24 und 48 Stunden, verglichen mit der periduralen. Eine periphere Wirkung des Morphiums auf die Harnblase ist möglich und der Wirkungsmechanismus wird diskutiert.

## RETENCION DE ORINA DURANTE LA ANALGESIA CON MORFINA ADMINISTRADA INTRAMUSCULAR Y EXTRADURALMENTE

### SUMARIO

Cincuenta y seis pacientes sanos sometidos a colecistectomia u operaciones de úlcera del duodeno, recibieron un "alto nivel" de morfina administrada intramuscularmente o un "bajo nivel" de morfina administrada extraduralmente, ambas durante el periodo posoperativo y de forma aleatoria. El 35% del grupo de administración intramuscular, el 33% del de "alto nivel" y el 50% del de "bajo nivel" sufrieron retención de orina, presentándose este hecho durante las primeras 24 horas en todos los grupos. La dosis media acumulativa de morfina necesaria para aliviar el dolor, quedó en la misma gama para todos los grupos (13,4 a 16,5 mg) durante las 2 primeras horas de terapia, mientras que las cantidades fueron de entre dos y cuatro veces superiores después de 24 y de 48 horas, al compararse el grupo de administración intramuscular con el de la ruta extradural. Es posible el efecto periférico de la morfina en la vejiga de la orina y se discute el mecanismo de la actividad.

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# EFFECT OF POSTURE AND SOME C.S.F. CHARACTERISTICS ON SPINAL ANAESTHESIA WITH ISOBARIC 0.5% BUPIVACAINE

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## SUMMARY

The effect of the sitting position (0, 2.5, 5.0 or 7.5 min), during and after the injection of 3 ml of 0.5% isobaric bupivacaine-HCl, on the segmental spread of spinal analgesia was studied in 40 patients. Ten patients injected in the lateral horizontal position acted as controls. The spread of analgesia was significantly greater in those who sat for 2.5 min or more compared with those who were immediately put in the supine position. Prolongation of the sitting time did not produce a higher analgesic block. The motor block was complete in all patients; its duration was significantly longer in the horizontal group than in all the sitting groups. There was no significant correlation between the different c.s.f. indices (pressure, protein and chloride ion concentration, pH, and specific gravity) and the spinal block.

In a previous study we found that when patients were in a sitting position the spread of isobaric 0.75% bupivacaine analgesia was significantly greater compared with patients who were supine (Tuominen, Kalso and Rosenberg, 1982). A similar trend was seen with 0.5% bupivacaine. The sitting time was set at 2.5 min. The present study compares the influence of different sitting times on the spread and duration of spinal block.

The spread of spinal analgesia with isobaric bupivacaine may be influenced by a number of factors: bupivacaine has a high affinity for proteins; the pH of the cerebrospinal fluid (c.s.f.) affects the ionization of bupivacaine; the c.s.f. chloride concentration influences the osmotic equilibrium; the concentration of local anaesthetics in the c.s.f. is inversely proportional to the distance from the injection site; and it has been suggested that the c.s.f. pressure is inversely proportional to the height of the spinal block (Helrich et al., 1950; Lund, 1971; Covino and Vassallo, 1976; Lee and Atkinson, 1978).

## MATERIALS AND METHODS

### *Patients*

Informed verbal consent to the study was obtained from 50 orthopaedic patients. All were in good general health (ASA I–III, American Society of Anesthesiologists, 1963), co-operative, and were not taking drugs suspected of or known to modify the action of local anaesthetics. Premedication was oral diazepam 5–20 mg given 1.5–2 h before anaesthesia and i.m. atropine 0.01 $mg\,kg^{-1}$ about 1 h before anaesthesia.

### *Spinal anaesthesia*

Before the spinal injection Ringer solution 8 $ml\,kg^{-1}$ was rapidly infused into the blood stream. This same volume was also administered over a period of about 20 min after the injection of bupivacaine. The following values were determined (c.s.f. samples approximately 2 ml):

(1) Distance between the 3rd lumbar and 7th cervical spinal processes.
(2) C.s.f. pressure, with the patient in the block position.
(3) C.s.f. chloride concentration.
(4) C.s.f. pH (37 °C)
(5) C.s.f. protein concentration (Lowry et al., 1951).
(6) C.s.f. specific gravity by total solid meter.

After the c.s.f. sample had been taken, 3 ml of 0.5% isobaric bupivacaine-HCl (density at 37 °C 1.000 $g\,ml^{-1}$ (Astra Pharm. Comp., Södertälje, Sweden)) was injected over about 10 s into interspace L3–4 using a 25-gauge needle and barbotage.

The patients were randomly divided into four groups according to the sitting time. A fifth group of 10 patients injected in a lateral horizontal position was taken from consecutive patients known to have difficulty in sitting, and who were operated on during the period of the study. The study groups were:

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Group I: Spinal injection with the patient in a sitting position and immediately thereafter placed into a horizontal position.
Group II: Sitting for 2.5 min after the injection.
Group III: Sitting for 5.0 min after the injection.
Group IV: Sitting for 7.5 min after the injection.
Group V: Spinal injection with the patient in a lateral horizontal position.

### *Analgesia and motor block*

The segmental spread of analgesia was studied by pinprick using a short bevel 25-gauge needle, with the skin at the shoulder as the reference point. Testing was started immediately after placing the patient in the horizontal position and continued at 2-min intervals for 30 min. Regression of analgesia after surgery was tested at 30-min intervals until the first sacral spinal segment had recovered (end-point). Motor nerve block was evaluated at 2-min intervals using Bromage's score (0–3).

### *Haemodynamic and side-effects*

Arterial pressure and heart rate were measured at 5-min intervals during induction and during surgery, and at 15-min intervals during recovery. E.c.g. was monitored continuously.

In the ward, the occurrence of nausea or vomiting, hypotension, urinary problems was noted. The patients were interviewed on the 1st day after operation by one of the researchers, who tested skin sensation and motor function of the legs. Special emphasis was placed on evaluation of headache or backache.

The statistical significance of the differences between the means was estimated using Student's *t* test.

## RESULTS

There were no significant differences between the mean ages, weights or heights of the patients in each of the five groups. The distances measured from the third lumbar process to the 7th cervical process did not differ significantly (table I). No linear correlation was found between c.s.f. pressures in the sitting position and the distances between L3 and C7.

Furthermore, there were no significant differences between c.s.f. characteristics (table II). However, some interesting individual variations were noted. The smallest protein content was 0.20 mg $ml^{-1}$ in a patient in group II (analgesia spread T2) and the greatest 0.80 mg $ml^{-1}$ in a patient in group III (analgesia spread T4). The smallest chloride content was 117 mmol $litre^{-1}$ in a group V patient (T5) and the greatest 136 mmol $litre^{-1}$ in a group II patient (T11). The specific gravity of the c.s.f. was 1.004, except in 10 cases: 1.000 (T4), 1.001 (T2) and 1.011 (T11) in group IV patients; and 1.002 (T4) in a patient from group V; six further patients had a c.s.f. specific gravity of 1.003.

The spread of analgesia was significantly greater ($P < 0.01$) in groups II, III and IV than in group I (fig. 1). The difference between groups IV and I was statistically significant at 10 min and thereafter. Between groups III and I the difference was significant at 8 min and after that only at 30 min. The prolongation of the time of sitting after the injection did not produce a higher analgesic block: there were no significant differences between groups II, III and IV. Neither were there any significant differences between group V (horizontal) and the seated groups I, II, III and IV.

The mean time until complete analgesia was shor-

TABLE I. *Mean age, weight, height and c.s.f. pressure of patients and the distance from L3 to C7 in each group (ranges in parentheses)*

| Group | Sex F/M | Age (yr) | Weight (kg) | Height (cm) | C.s.f. pressure (cm $H_2O$) | L3–C7 (cm) |
|---|---|---|---|---|---|---|
| I<br>Sitting 0 min | 7/3 | 59<br>(43–72) | 76<br>(63–100) | 166<br>(155–187) | 35.6<br>(20.5–47.5) | 44<br>(38–49) |
| II<br>Sitting 2.5 min | 5/5 | 53<br>(40–65) | 71<br>(57–89) | 166<br>(154–181) | 35.5<br>(26.0–46.5) | 44<br>(41–51) |
| III<br>Sitting 5.0 min | 7/3 | 62<br>(46–71) | 72<br>(55–97) | 163<br>(156–174) | 35.3<br>(14.0–45.0) | 44<br>(38–48) |
| IV<br>Sitting 7.5 min | 6/4 | 57<br>(44–72) | 72<br>(54–102) | 164<br>(150–174) | 33.0<br>(15.5–41.0) | 43<br>(40–53) |
| V<br>Horizontal | 7/3 | 64<br>(48–75) | 67<br>(59–90) | 165<br>(149–182) | 17.3<br>(8.0–29.0) | 44<br>(39–50) |

TABLE II. *Mean protein and chloride-ion concentration, pH and specific gravity of c.s.f. in each group (ranges in parentheses)*

| Group | Protein concn (mg ml$^{-1}$) | Cl$^{-}$ concn (mmol litre$^{-1}$) | pH (units) | Specific gravity |
|---|---|---|---|---|
| I<br>Sitting 0 min | 0.38<br>(0.25–0.65) | 125<br>(123–127) | 7.35<br>(7.30–7.38) | 1.004<br>(1.003–1.004) |
| II<br>Sitting 2.5 min | 0.38<br>(0.2. –0.48) | 126<br>(121–136) | 7.34<br>(7.31–7.38) | 1.004<br>(1.003–1.004) |
| III<br>Sitting 5.0 min | 0.48<br>(0.34–0.80) | 127<br>(121–135) | 7.34<br>(7.29–7.40) | 1.004<br>(1.004–1.004) |
| IV<br>Sitting 7.5 min | 0.41<br>(0.25–0.57) | 127<br>(124–132) | 7.34<br>(7.32–7.37) | 1.004<br>(1.000–1.011) |
| V<br>Horizontal | 0.39<br>(0.28–0.59) | 125<br>(117–129) | 7.36<br>(7.30–7.49) | 1.004<br>(1.002–1.004) |

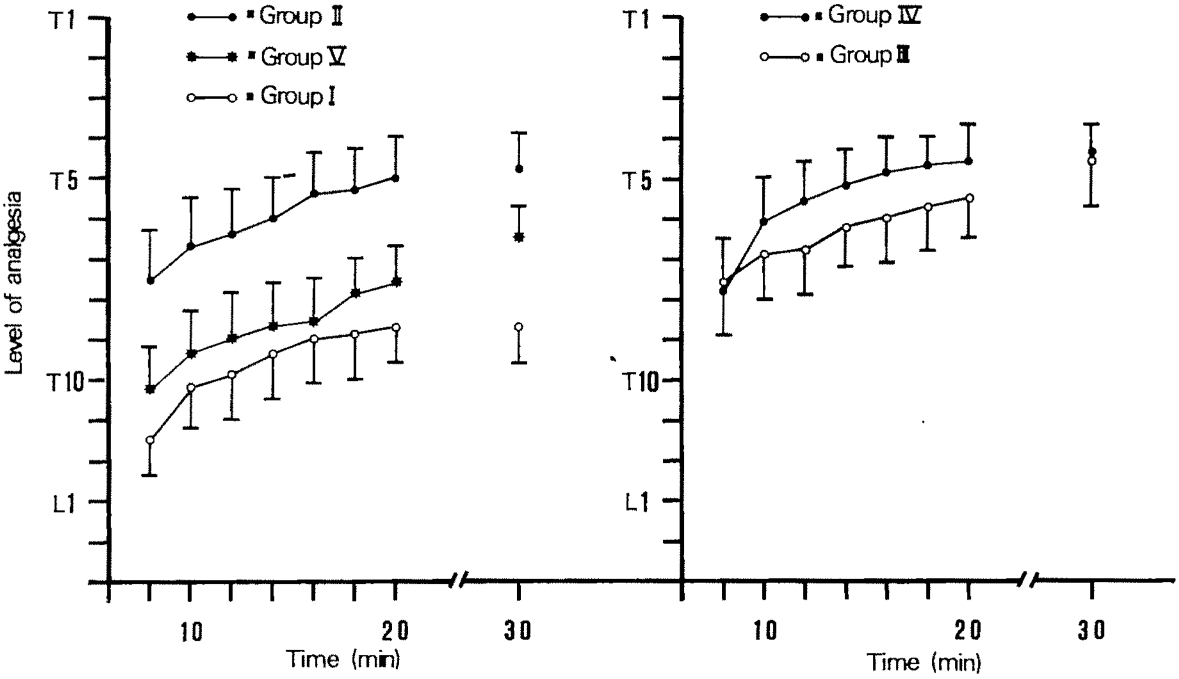

FIG. 1. Mean levels of pinprick analgesia following intrathecal injection of 0.5% isobaric bupivacaine 3 ml in the different sitting groups (I–IV) and the horizontal group (V). SEM bars have been drawn only in one direction for easier distinction of the curves.

ter in the sitting groups than in the horizontal, but the difference was not significant. Furthermore, there were no significant differences between the duration of analgesia in groups I–V (table III).

There were no statistically significant correlations between the segmental spread of pinprick analgesia and any of the c.s.f. characteristics measured. The best relationship found was an inverse correlation between the segmental spread of pinprick analgesia at 10 min and the protein concentration in group V ($r = -0.52$). Interestingly, the greatest mean protein concentration (0.48 mg ml$^{-1}$) was found in group III, in which the maximum pinprick analgesia was lower than in group II, in which the protein concentration was 0.38 mg ml$^{-1}$.

Motor block in the legs was complete in all patients. The shortest time of onset of complete motor block was in group V and there was a significant ($P < 0.05$) difference between groups V and II (table III). The time interval from Bromage's score 3 to score 0 was longest in group V. The difference was significant between groups V and II ($P < 0.02$) and between groups V and III, and V and IV ($P < 0.05$). In the horizontal group there was an inverse relationship between the height of pinprick analgesia and the duration of motor block, but the correlation was not statistically significant.

The mean decreases in arterial systolic pressure during induction were 9%, 15%, 22%, 18% and 20% of the initial pressures in groups I, II, III, IV and V, respectively. The differences were significant between groups I and III and I and V ($P < 0.05$). Decreases of more than 30% were measured in groups III (two patients), IV (two patients) and V (three patients); the most marked decreases, 36% and 50%, were both in group III. A correlation between the height of the sensory block and the decrease in arterial systolic pressure during induction was evident only in group V ($r = 0.75$, $P < 0.05$).

The frequency of side-effects in the recovery room and during the first day after operation was small in each group. Three patients complained of headache. In no case was it typical "spinal" headache, and all recovered without special treatment. Eleven patients vomited, four of whom were in group IV. Two patients in each of the groups I, III and V also suffered episodes of vomiting after operation. Also, four of the five patients who had difficulty with micturition were from group IV. Another patient with micturition problems was from group II. One patient (group IV) complained of hyperalgesia of the segments which had been anaesthetized.

## DISCUSSION

This study confirmed the general clinical impression that "isobaric" bupivacaine acts as if it were slightly hypobaric. The specific gravity of bupivacaine-HCl is 1.004 at 20 °C, which is equal to that of the c.s.f. at the same temperature. At 37 °C the specific gravity of the commercial isobaric bupivacaine-HCl is 1.000. The specific gravity of one c.s.f. sample was the same (1.004) at both temperatures.

We tried to standardize most of the important factors suggested or shown to influence the spread of spinal analgesia—the site and the speed of injection, the type of spinal needle (Neigh, Kane and Smith, 1970), barbotage and positioning of the patient dur-

TABLE III. *Characteristics of the spinal block (means ± SEM in parentheses). Duration of pinprick = interval from maximum pinprick analgesia to the recovery of S1 segment. Duration of motor block = interval from Bromage's score 3 back to score 0*

| Group | Pinprick analgesia at 10 min | Max. pinprick analgesia | Time to max. pinprick (min) | Time to max. motor block (min) | Duration of pinprick (min) | Duration of motor block (min) |
|---|---|---|---|---|---|---|
| I | 12.8 = T10 | 14.3 = T9 | 16.6 | 11.0 | 337 | 258 |
| Sitting 0 min | (1.0) | (0.9) | (1.3) | (1.7) | (23) | (17) |
| II | 16.3 = T7 | 18.2 = T5 | 17.2 | 16.2 | 333 | 241 |
| Sitting 2.5 min | (1.2) | (0.9) | (2.5) | (2.5) | (19) | (17) |
| III | 16.1 = T7 | 18.4 = T5 | 18.2 | 13.6 | 346 | 251 |
| Sitting 5.0 min | (1.1) | (1.0) | (2.8) | (2.2) | (30) | (19) |
| IV | 17.0 = T6 | 18.6 = T4 | 15.2 | 14.2 | 326 | 244 |
| Sitting 7.5 min | (1.0) | (0.9) | (1.6) | (2.8) | (22) | (24) |
| V | 13.6 = T9 | 16.5 = T6 | 20.8 | 9.4 | 334 | 310 |
| Horizontal | (1.1) | (0.8) | (2.8) | (1.7) | (23) | (19) |

ing injection (Lund, 1971), the total volume of the anaesthetic agent (Nolte and Stark, 1979). The variable in this study was therefore the time which the patient remained sitting after the injection (groups I–IV). The maximal pinprick analgesia was on average 3–4 segments higher when the patient remained in the sitting position for 2.5–7.5 min than when the patient was immediately put into the supine position. Although there was a statistically significant difference in the maximal spread this may lack clinical importance. The fact that the prolongation of the time of sitting did not produce a higher level of analgesia may have been the result of a rapid osmotic equilibrium of bupivacaine-HCl with the c.s.f. and the distance-dependent dilution effect (Helrich et al., 1950).

Interestingly, there were no significant differences between the spread of analgesia in the horizontal group V and that in groups II–IV. This result is analogous with that found in a previous study (Tuominen, Kalso and Rosenberg, 1982). The mean segmental spread of analgesia in comparable groups in our present study was slightly higher, which may be explained by the longer testing time (up to 30 min). Chambers and others (1982) have also indicated that the segmental spread of analgesia with intrathecal bupivacaine is not always complete within 20 min. The explanation for the difference in spread between groups I and V may be related to c.s.f. pressure. The abrupt decrease in the lumbar c.s.f. pressure when moving from a sitting to a supine position immediately after bupivacaine injection in group I probably caused a caudally-directed c.s.f. flow and a lower bupivacaine block.

A pressure change occurring after 2.5 min or later no longer seemed to inhibit the segmental cranial spread. The c.s.f. pressure values were least in the horizontal patients (group V) and were probably very little affected by posture changes. However, in spite of this there was no correlation between the spread of analgesia and the c.s.f. pressure in this group. The different chemical characteristics of the c.s.f. seem to have little effect on the spread of spinal analgesia with 0.5% bupivacaine-HCl. As bupivacaine has a high affinity for proteins, one might assume that patients with a high protein content in the c.s.f. would have a lower segmental spread of analgesia. The mean protein concentration was greatest (0.48 $\mathrm{mg\,ml^{-1}}$) in group III, where the mean spread of analgesia was lower than that in group II (0.38 $\mathrm{mg\,ml^{-1}}$). However, the patient with the greatest protein content of 0.80 $\mathrm{mg\,ml^{-1}}$ was from group III and the segmental spread of analgesia appeared to be quite normal (T5 at 10 min and T4 at 30 min).

The motor blocks were complete, substantiating the findings of earlier studies using 3 ml of isobaric 0.5% bupivacaine (Chambers, Edström and Scott, 1981; Tuominen, Kalso and Rosenberg, 1982). The period required to complete the motor block was shortest in the horizontal group. On the other hand, the duration of the motor block was longest in the horizontal groups of both studies. The concentration of the anaesthetic in the nervous tissue in the vicinity of the injection site (L3–4) remained greatest in these patient groups, which probably explains the long duration before the patients were able to raise an extended leg (Bromage's score 0). A similar observation on the differences in the duration of motor block has also been made when a greater concentration (Tuominen, Kalso and Rosenberg, 1982) or hyperbaric bupivacaine (Chambers et al., 1982) has been used.

The standardized i.v. fluid regimen at the beginning of anaesthesia (almost 1 litre of Ringer solution within 20–30 min for a patient weighing 60 kg) might explain the absence of severe hypotensive complications in this study. Hypotension is probably a triggering factor for nausea, vomiting and micturition difficulties (Lund, 1971). In fact, the frequency of these complications was greater in group III, where the decrease in arterial pressure was greatest, too. On the whole the frequency of any complication was very small and, like Nightingale and Marstrand (1981), we find spinal anaesthesia with isobaric 0.5% bupivacaine particularly suitable for orthopaedic operations in elderly patients. We also conclude that the segmental spread of analgesia and the duration of motor block of the lower extremities may be roughly predicted by having the patient in a predetermined position at the time of injection of isobaric bupivacaine. A sitting time longer than 2.5 min did not give any advantage of extension of spread of analgesia.

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## REFERENCES

Chambers, W. A., Edström, H. H., and Scott, D. B. (1981). Effect of baricity on spinal anaesthesia with bupivacaine. *Br. J. Anaesth.*, 53, 279.

——Littlewood, D. G., Edström, H. H., and Scott, D. B. (1982). Spinal anaesthesia with hyperbaric bupivacaine: Effects of concentration and volume administered. *Br. J. Anaesth.*, 54, 75.

Covino, B. G., and Vassallo, H. G. (1976). *Local Anesthetics: Mechanisms of Action and Clinical Use*, chapters 4 and 5. New York, San Francisco, London: Grune & Stratton.

Helrich, M., Papper, E. M., Grodie, B. B., Fink, M., and Rovenstine, E. A. (1950). Fate of intrathecal procaine and spinal fluid level required for surgical anesthesia. *J. Pharmacol. Exp. Ther.*, 100, 78.

Lee, J. A., and Atkinson, R. S. (1978). Sir Robert Macintosh's *Lumbar Puncture and Spinal Analgesia, Intradural and extradural*, p. 75. Glasgow: Churchill Livingstone.

Lowry, O. H., Rosenbrough, N. J., Farr, A. L., and Randall, R. J. (1951). Protein measurement with the Folin phenol reagent. *J. Biol. Chem.*, 193, 265.

Lund, P. C. (1971). *Principles and Practice of Spinal Anesthesia*, chapter III. Springfield, Illinois: Charles C. Thomas.

Neigh, J. L., Kane, P. B., and Smith, T. C. (1970). Effects of speed and direction of injection on the level and duration of spinal anesthesia. *Anesth. Analg. (Cleve.)*, 49, 912.

Nightingale, P. J., and Marstrand, T. (1981). Subarachnoid anaesthesia with bupivacaine for orthopaedic procedures in the elderly. *Br. J. Anaesth.*, 53, 369.

Nolte, H., and Stark, P. (1979). Die Dosis-Wirkungsrelation des isobaren Bupivacain zur Spinalanaesthesie. *Regional-Anaesthesie*, 2, 1.

Tuominen, M. K., Kalso, E. A., and Rosenberg, P. H. (1982). The effect of posture on the spread of spinal anaesthesia with isobaric 0.75% or 0.50% bupivacaine *Br. J. Anaesth.*, 54, 313.

## EFFETS DE LA POSTURE ET DE CERTAINES CARACTERISTIQUES DU LCR SUR LA RACHIANESTHESIE A LA BUPIVACAINE ISOBARE A 0,5%

### RESUME

On a étudié l'effet de la position assise (0; 2,5; 5,0 ou 7,5 min) pendant et après l'injection de 3 ml de bupivacaïne-HCl isobare sur la diffusion segmentaire de la rachianesthésie chez 40 patients. Dix patients on reçu leur injection en décubitus latéral et ont servi de témoins. La diffusion de l'analgésie était significativement plus grande chez ceux qui restaient assis 2,5 min ou plus par rapport à ceux que l'on allongeait immédiatement. La prolongation de la position assise n'entraînait pas de bloc sensitif plus important. Le bloc moteur était total chez tous les patients. Sa durée était significativement plus longue chez les témoins allongés que chez tous les patients assis. Il n'y avait pas de corrélation significative entre les différents paramètres du LCR (pression, concentration en protéines et en ions chlorures, pH et poids spécifique) et la rachianesthésie.

## DIE AUSWIRKUNG DER LAGERUNG UND EINIGER LIQUOREIGENSCHAFTEN AUF DIE SPINALANÄSTHESIE MIT ISOBAREM 0,5% BUPIVAKAIN

### ZUSAMMENFASSUNG

Die Auswirkung der Sitzposition (0, 2,5, 5 oder 7,5 min) während und nach der Injektion von 3 ml 0,5% isobarem Bupivakainhydrochlorid auf die segmentale Ausbreitung der Spinalanästhesie wurde an 40 Patienten untersucht. Zehn Patienten, bei denen die Injektion in Seitenlage vorgenommen wurde, dienten als Kontrollgruppe. Die Ausbreitung der Analgesie war bei 2,5 min und längerem Sitzen signifikant größer als bei jenen, die sofort in die Rückenlage gebracht wurden. Längeres Sitzen verursachte keine höhere Blockade. Die Motor-blockade war bei allen Patienten vollständig. Ihre Dauer war bei der Horizontalposition signifikant länger als in allen Sitz-Gruppen. Es bestand keine signifikante Korrelation zwischen den verschiedenen Liquor-Eigenschaften (Druck, Eiweiss, Chloridionenkonzentration, dem pH und dem spezifischen Gewicht) und dem Spinalblock.

## EFECTO DE LA POSTURA Y ALGUNAS CARACTERÍSTICAS C.S.F. SOBRE LA ANESTESIA ESPINAL CON BUPIVACAINA ISOBÁRICA AL 0,5%

### SUMARIO

Se llevó a cabo un estudio en 40 pacientes del efecto de la postura sentada (0, 2,5, 5,0 y 7,5 min) durante y después de la inyección de 3 ml de bupivacaina-HCl isobárica al 0,5% en la difusión fragmentaria de la analgesia espinal. Diez pacientes a los cuales se hizo la inyección en postura lateral horizontal actuaron como controles. La difusión de la analgesia fue mucho major en los que permanecieron sentados durante 2,5 min ao más en comparación con los que se pusieron de inmediato en postura supina. La prolongación del tiempo de sentada no produjo un bloqueo analgésico mayor. El bloqueo motor fue total en todos los pacientes; su duración fue significativamente más larga en el grupo horizontal que en los grupos en postura sentada. No hubo ninguna correlación significativa entre los distintos índices C.S.F. (presión, concentración en proteinas y del ion de cloruro, pH y gravedad específica) y el bloqueo espinal.

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# CARDIOVASCULAR EFFECTS OF ALFENTANIL ANAESTHESIA

P. S. SEBEL, J. G. BOVILL AND A. VAN DER HAVEN

## SUMMARY

In 30 patients undergoing cardiac surgery, anaesthesia was induced with alfentanil 125 $\mu g\,kg^{-1}$ and maintained with an infusion of alfentanil 0.5 $mg\,kg^{-1}\,h^{-1}$ until the start of cardiopulmonary bypass, and alfentanil 0.25 $mg\,kg^{-1}\,h^{-1}$ thereafter until the end of surgery. Pancuronium was given and the lungs ventilated with air in oxygen. In the majority of patients, there were no significant changes in cardiovascular measurements throughout the study, although two received sodium nitroprusside for the control of hypertension, and in one patient hypertension was so severe that the method of anaesthesia was abandoned. Transient hypotension occurred on induction in one patient. Twenty-six patients required alfentanil supplementation before bypass. These results indicate that anaesthesia with an alfentanil infusion provides satisfactory cardiovascular stability for cardiac surgery.

Alfentanil is a chemically novel, potent, extremely short-acting opioid analgesic. Its animal pharmacology was described in 1981 (Niemegeers and Janssen, 1981). In the tail withdrawal reaction test in rats it is 73 times as potent as morphine. The therapeutic ratio is very high, $LD_{50}/ED_{50}$ being 1080 (morphine and fentanyl have therapeutic ratios of 70 and 227 respectively). At twice the smallest $ED_{50}$ alfentanil has a duration of action of 10 min (morphine and fentanyl have durations of action of 120 min and 35 min respectively). This apparent short duration of action is in keeping with its short terminal elimination half-life in man of 83 min (Bovill et al., 1981) compared with fentanyl, 219 min (McClain and Hug, 1980). However, pharmacokinetic data for alfentanil from dogs give conflicting results, with a terminal elimination half-life of 134 min (Borel et al., 1981).

In human volunteers, alfentanil 6.4 $\mu g\,kg^{-1}$ produced respiratory depression (ventilatory response to carbon dioxide) for 30–50 min (Kay and Pleuvry, 1980). Alfentanil has been used in man for supplementation of anaesthesia (Kay and Stephenson, 1980; Van Leeuwen and Deen, 1981; Van Leeuwen, Deen and Helmers, 1981). It has been found to give good cardiovascular stability when used as an induction agent (Spierdijk et al., 1980; Nauta et al., 1981). It has also been used as a complete anaesthetic for coronary artery surgery, both as frequent bolus injections (De Lange, Stanley and Boscoe, 1981) and continuous infusion (De Lange, De Bruijn et al., 1981).

Opioid analgesics have been used as anaesthetic agents in cardiac surgery because of the good cardiovascular stability that can be obtained. However, hypertensive responses can occur, especially after sternotomy (Sebel et al., 1982a). Maintaining a high blood concentration of the opioid may reduce the risk of hypertension. In this study we have investigated the cardiovascular effects of a continuous alfentanil infusion to determine if good cardiovascular stability is obtained and if hypertensive responses are reduced.

## METHOD

Thirty adults undergoing elective cardiac surgery gave informed consent to the investigation (table I). Patients undergoing coronary artery surgery were taking beta-blocking drugs, which were discontinued on the evening before surgery.

The day before operation, all patients had a flow-

TABLE I. *Patient data*

| | |
|---|---|
| No. of patients (M/F) | 30 (23/7) |
| Weight (kg) (mean ± SEM) | 75.6 ± 1.96 |
| Age (yr) (mean ± SEM) | 54.9 ± 1.61 |
| Type of surgery | |
| Coronary artery | 26 |
| Aortic valve | 2 |
| Coronary artery and aortic valve | 1 |
| Open mitral valvotomy | 1 |

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directed pulmonary artery (Swan–Ganz) catheter inserted (under fluoroscopic control) via the subclavian vein. Premedication was lorazepam 4–5 mg orally 1.5 h before operation. In the operating theatre e.c.g. leads were applied, two large-gauge peripheral venous cannulae and an 18-French gauge radial arterial cannula were inserted under local analgesia. After preoxygenation, pancuronium 2 mg was injected i.v. followed by alfentanil 125 $\mu g\,kg^{-1}$ given over 2 min. During the injection of alfentanil a further 6 mg of pancuronium was given in divided doses when the patient became unresponsive to commands. After the initial dose of alfentanil an infusion was commenced at a rate of 0.5 $mg\,kg^{-1}\,h^{-1}$ delivered via an IVAC 630 volumetric infusion pump. Five minutes after the start of induction, the patient's trachea was intubated. Ventilation was continued with air in oxygen ($F\text{I}_{O_2}$ 0.5). Ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 4.5–5%. Persistent hypertension (an increase in systolic pressure more than 20% above control) was treated with a bolus injection of alfentanil 2.5 mg, repeated up to four times for each episode of hypertension (up to a total of 10 mg). If this did not control the arterial pressure, sodium nitroprusside (SNP) 10–100 $\mu g\,min^{-1}$ was given by continuous i.v. infusion. At the start of cardiopulmonary bypass the alfentanil infusion rate was reduced by half to 0.25 $mg\,kg^{-1}\,h^{-1}$ and continued at this rate until the end of surgery.

During anaesthesia and surgery, e.c.g., heart rate, systolic and diastolic arterial pressures and central venous pressure were monitored continuously. The output from the arterial pressure module (Hewlett–Packard) was connected to a Philips Cardiac Output Computer. The computer calculates the stroke volume on a beat-to-beat basis using the characteristic impedance pulse contour method (Wesseling et al., 1974).

Calibration factors are included in the computer program to correct for changes in mean arterial pressure and heart rate and for changes in aortic impedance with age. This method of pulse contour analysis correlates well with conventional methods of cardiac output determination even during marked change in arterial pressure, heart rate or systemic vascular resistance or during arrhythmia (Wesseling et al., 1976; Thomas, 1978). Although designed for use with a pressure waveform derived from the central aorta, it has been shown that the results are also reliable with brachial or radial artery pressure as used in the study (Smith et al., 1974). To obtain absolute values for cardiac output using pulse contour analysis, it is necessary to precalibrate the computer. This was done using thermodilution cardiac output measurements. The Philips cardiac output computer was calibrated to the mean of two consecutive thermodilution measurements that were within 10% of each other. Systolic, diastolic and right atrial pressures, heart rate, cardiac output, pulmonary artery and pulmonary capillary wedge pressures were recorded every minute. Derived cardiovascular indices were calculated using standard formulae. Fluid administered in the period before cardiopulmonary bypass was restricted to 5% glucose 300–500 ml.

Data are presented as mean values ± SEM. Analysis of variance was used to determine significance of changes within groups. A modified *t* test was used to identify significant differences from control values using critical values for *P* calculated according to the method of Bonnferroni (Wallenstein, Zucker and Fleiss, 1980).

## RESULTS

As it is impossible to present numerical cardiovascular data for each minute of anaesthesia and surgery, data related to points of maximum stimulation are shown in table II. There were no statistically significant changes in any of the measured or derived cardiovascular indices at any point during the study compared with pre-induction values.

Data more than 10 min after sternotomy are not reported because of wide variations in measured values following surgical manipulation of the heart.

Twenty-six of the 30 patients required alfentanil supplementation before the start of cardiopulmonary bypass. The mean total supplementary dose before bypass of 110.6 ± 16.97 $\mu g\,kg^{-1}$ (range 31–263 $\mu g\,kg^{-1}$) and the mean total dose before bypass (induction + infusion + supplements) was 892.2 ± 38.84 $\mu g\,kg^{-1}$. In two patients supplementary doses of alfentanil failed to control the arterial pressure adequately (according to the criteria described) and in both patients control of pressure was achieved by an infusion of SNP. After cardiopulmonary bypass eight patients required alfentanil supplements, mean dose 82.3 ± 20.46 $\mu g\,kg^{-1}$ (range 61.2–211.6 $\mu g\,kg^{-1}$). The mean total dose for the period of surgery including induction dose was 1526.6 ± 405.29 $\mu g\,kg^{-1}$ (range 996.8–2250.2 $\mu g\,kg^{-1}$) which, taking into account the duration of surgery, is 6.7 ± 0.41 $\mu g\,kg^{-1}\,min^{-1}$ dose requirement. After bypass four patients received dopamine

TABLE II. *Cardiovascular variables in 30 patients receiving alfentanil with air in oxygen (mean ±SEM)*

| | | Induction | | Intubation | | Before incision | Incision | | Sternotomy | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Control | +2 min | +5 min | +2 min | +5 min | | +2 min | +5 min | +2 min | +5 min | +10 min |
| Systolic pressure (mm Hg) | 140.0<br>±4.86 | 124.8<br>±6.36 | 124.7<br>±6.27 | 135.5<br>±5.78 | 122.7<br>±5.84 | 125.9<br>±4.67 | 131.9<br>±6.48 | 143.0<br>±4.29 | 140.4<br>±6.85 | 143.3<br>±6.29 | 146.6<br>±6.02 |
| Diastolic pressure (mm Hg) | 73.8<br>±2.10 | 69.7<br>±2.21 | 70.1<br>±2.54 | 73.3<br>±2.52 | 71.2<br>±2.10 | 70.7<br>±2.10 | 76.7<br>±2.40 | 79.9<br>±2.50 | 80.3<br>±2.35 | 81.2<br>±2.62 | 81.2<br>±2.40 |
| Mean pressure (mm Hg) | 95.9<br>±2.64 | 88.0<br>±3.17 | 88.3<br>±3.58 | 94.0<br>±3.20 | 88.4<br>±2.57 | 89.1<br>±2.80 | 95.1<br>±3.37 | 100.9<br>±2.83 | 100.4<br>±2.97 | 101.9<br>±3.21 | 103.0<br>±3.13 |
| Central venous pressure (mm Hg) | 1.3<br>±0.66 | 3.2<br>±0.99 | 2.7<br>±0.93 | 2.4<br>±0.97 | 2.4<br>±1.10 | 2.4<br>±0.95 | 2.7<br>±0.93 | 2.5<br>±0.92 | 1.5<br>±0.90 | 1.20<br>±0.92 | 0.82<br>±0.99 |
| Heart rate (beat $min^{-1}$) | 71.6<br>±1.93 | 75.2<br>±2.11 | 79.8<br>±3.25 | 83.8<br>±3.52 | 78.5<br>±3.82 | 71.5<br>±3.58 | 73.7<br>±3.67 | 78.3<br>±3.04 | 80.7<br>±3.16 | 82.4<br>±3.07 | 82.9<br>±3.82 |
| Pulmonary arterial pressure (mm Hg) | 14.1<br>±1.08 | 15.1<br>±0.95 | 14.6<br>±0.99 | 15.7<br>±1.28 | 13.8<br>±1.13 | 13.26<br>±1.00 | 14.5<br>±1.18 | 14.7<br>±1.32 | 14.0<br>±1.30 | 13.7<br>±1.29 | 14.2<br>±1.46 |
| Pulmonary capillary wedge pressure (mm Hg) | 5.1<br>±0.86 | 7.0<br>±1.00 | 6.4<br>±1.15 | 5.8<br>±0.76 | 4.5<br>±0.96 | 5.9<br>±0.97 | 5.7<br>±0.84 | 6.2<br>±1.05 | 6.1<br>±0.99 | 4.6<br>±1.03 | 7.5<br>±1.39 |
| Cardiac index (litre $min^{-1}$ $m^{-2}$) | 3.6<br>±0.18 | 3.2<br>±0.21 | 3.4<br>±0.28 | 3.7<br>±0.38 | 3.5<br>±0.27 | 3.0<br>±0.20 | 3.1<br>±0.18 | 3.3<br>±0.18 | 3.6<br>±0.24 | 3.7<br>±0.23 | 3.6<br>±0.21 |
| Stroke index (ml $beat^{-1}$ $m^{-2}$) | 50.6<br>±2.70 | 42.7<br>±2.86 | 43.6<br>±3.32 | 44.0<br>±3.50 | 44.7<br>±3.56 | 41.7<br>±1.87 | 41.0<br>±1.9 | 42.9<br>±2.61 | 45.7<br>±3.13 | 46.3<br>±3.18 | 45.8<br>±3.15 |
| Rate–pressure product | 10086<br>±493.4 | 9413<br>±576.0 | 10182<br>±947.0 | 11511<br>±829.1 | 9360<br>±579.8 | 9061<br>±600.1 | 9816<br>±720.8 | 11231<br>±568.7 | 11398<br>±821.8 | 11936<br>±774.3 | 12022<br>±792.2 |
| Peripheral resistance (dyne s $cm^{-5}$) | 1118<br>±47.1 | 1159<br>±58.2 | 1097<br>±55.7 | 1149<br>±73.3 | 1121<br>±66.7 | 1283<br>±62.0 | 1337<br>±99.3 | 1337<br>±99.3 | 1248<br>±74.7 | 1220<br>±75.7 | 1215<br>±127.2 |
| Left ventricular stroke work index (gm $mm^{-2}$ $beat^{-1}$) | 66.9<br>±2.76 | 50.9<br>±4.00 | 55.7<br>±7.47 | 47.32<br>±4.59 | 53.5<br>±5.11 | 53.1<br>±4.60 | 54.7<br>±4.21 | 57.3<br>±3.89 | 65.0<br>±6.36 | 70.3<br>±5.42 | 68.3<br>±6.57 |
| Pulmonary vascular resistance (dyne s $cm^{-5}$) | 94.9<br>±18.30 | 105.3<br>±24.77 | 102.6<br>±17.47 | 93.4<br>±22.66 | 93.0<br>±9.21 | 97.9<br>±13.00 | 90.4<br>±8.52 | 80.5<br>±9.70 | 72.9<br>±6.02 | 71.6<br>±10.28 | 80.7<br>±17.30 |

for inotropic support for periods of 10–60 min. Considering data from individual patients, one patient had a marked decrease in arterial pressure on induction, from 135 to 90 mm Hg systolic. Another patient, who was excluded from the study, became markedly hypertensive on induction of anaesthesia—the systolic pressure increased from a control value of 165 mm Hg to a peak of 220 mm Hg despite doubling the induction dose ($250\,\mu g\,kg^{-1}$). The patient received droperidol 10 mg, fentanyl 1 mg and the arterial pressure then decreased to less than control. Apart from those described above, no anaesthetic adjuvants were used. One patient did not survive cardiopulmonary bypass. Following direct questioning 4–5 days after surgery, none of the remaining 29 patients reported awareness.

## DISCUSSION

The use of opioid analgesics as anaesthetics, the problems of the use of "narcotic anaesthetics" and possible future developments have been reviewed recently (Lowenstein and Philbin, 1981). They discuss the issues of the e.e.g. response and relationship to unconsciousness and anaesthesia, chest wall rigidity, haemodynamic responses to induction, anaesthetic adjuvants and surgical stimulation, metabolic response and histamine release. The development of new techniques with opioid analgesics should be considered in relation to these issues.

Alfentanil is unique in that it is the shortest-acting potent opioid analgesic known. In animals it has a duration of action of 10 min (Niemegeers and Janssen, 1981) and, as an analgesic supplement for balanced anaesthesia, it is much shorter acting than fentanyl (Van Leeuwen, Deen and Helmers, 1981). These observations are in keeping with pharmacokinetic data obtained in man (Bovill et al., 1981). This renders alfentanil suitable for administration by continuous infusion, thus maintaining continuous high plasma alfentanil concentrations. This may be potentially beneficial in reducing haemodynamic responses to surgical stimulation which occur during cardiac surgery in up to 50% of patients anaesthetized with fentanyl $60–70\,\mu g\,kg^{-1}$ (Sebel et al., 1982a; Waller et al., 1981). One of the problems in assessing responses to different anaesthetic techniques is that slight variations in method of administration between institutions may result in marked differences in results. We have assessed the results of anaesthesia with fentanyl 60–70 $\mu g\,kg^{-1}$ (Sebel et al., 1982a) and sufentanil 15 $\mu g\,kg^{-1}$ (Sebel and Bovill, 1982) given under similar circumstances in the same institution; thus comparisons may be drawn, although a control group was not used in this study.

Chest wall rigidity may be expected in all patients if anaesthesia is induced with fentanyl alone (Waller et al., 1981). In none of our studies, including this one, have we experienced severe chest wall rigidity (as indicated by serious difficulty in manual ventilation) probably as a result of pretreatment with pancuronium 2 mg. While reducing the occurrence of severe chest wall rigidity, pancuronium will offset the bradycardia that may result from opioid administration (Lowenstein and Philbin, 1981). Alternatively, atropine may be given (Stanley and Webster, 1978). In our hands, chest wall rigidity and bradycardia are not major problems and there is little to choose between fentanyl, sufentanil and alfentanil.

The cardiovascular effects of alfentanil found in this study are similar to those reported by others for both frequent bolus injections (De Lange, Stanley and Boscoe, 1981) and infusion (De Lange, De Bruijn et al., 1981) and there appears to be little to choose between the three agents for cardiovascular stability during induction and intubation. In this study and with fentanyl 60–70 $\mu g\,kg^{-1}$ (Sebel et al., 1982a) there were no statistically significant changes in cardiovascular dynamics in response to induction and intubation. The group of patients anaesthetized with sufentanil (Sebel and Bovill, 1982) had a statistically significant decrease in arterial systolic pressure 5 min after induction and decreases in systolic and mean pressures and peripheral resistance just before incision. These were not associated with changes in stroke index or left ventricular stroke work index, so were not caused by myocardial depression; nor were they clinically troublesome. Since peripheral resistance decreased these cardiovascular changes may be a result of mild vasodilatation not seen with fentanyl or alfentanil.

With fentanyl 60–70 $\mu g\,kg^{-1}$, without further supplements, there was a 50% frequency of hypertension related to sternotomy (Sebel et al., 1982a). Similar findings were reported by Waller and others (1981). Increasing the fentanyl dose to 100–150 $\mu g\,kg^{-1}$ reduces this to about 10% (Sebel and Bovill, unpublished observations), making the results comparable to those with sufentanil following which 25% of patients required supplementation of anaesthesia and 10% required vasodilator therapy. In this study, 86% required supplementation and 7% vasodilator therapy. Thus, the infusion regimen used in this study was less adequate than a single injection of sufentanil in preventing hypertensive responses to noxious stimuli.

In one patient, who became hypotensive on induction, cardiac output was well maintained. The decrease in arterial pressure was probably a result of transient peripheral vasodilatation. The hypertensive episode in the patient who was excluded from the study is difficult to explain. This patient was not known to be a heavy user of alcohol or other drugs and was only moderately hypertensive before surgery. He may have had an episode of catecholamine release during induction, but we have no evidence to substantiate this.

One of the potential benefits of fentanyl anaesthesia is that it is capable of preventing hormonal responses to cardiac surgery, but not the catecholamine response to cardiopulmonary bypass (Stanley et al., 1980; Sebel et al., 1981). Sufentanil 20 $\mu g\,kg^{-1}$ produces similar suppression of hormonal responses to fentanyl, but will also suppress the antidiuretic hormone response to bypass (Sebel et al., 1982b) which fentanyl does not (Stanley, Philbin and Coggins, 1979). There is, as yet, limited information available about hormonal responses to alfentanil, but it appears to be as potent as sufentanil in blocking anti-diuretic hormone responses (De Lange, Stanley et al., 1981).

It is our practice to ventilate artificially the lungs of patients routinely for 24 h after cardiac surgery. Thus we did not investigate the recovery after alfentanil anaesthesia. De Lange and colleagues found that, after doses of alfentanil similar to those used in this study, the time to recovery was 1.5–4.4 h and to extubation was 3.5–6.0 h (De Lange, De Bruijn et al., 1981). This short recovery period will be of benefit where early removal of the endotracheal tube is considered desirable.

This study shows that alfentanil infusion provides good cardiovascular stability for anaesthesia for cardiac surgery. The results of our infusion regime yield little evidence to recommend alfentanil infusion rather than sufentanil or fentanyl anaesthesia. Areas for further study, where alfentanil as a complete anaesthetic may prove to be beneficial, include a higher dose regime, especially during the period of sternotomy, and further investigation of the time to recovery and adequate ventilation, as this may be significantly shorter than with other opioid analgesics.

## REFERENCES

Borel, J. D., Bentley, J. B., Gillespie, T. J., Gandolphi, A. J., and Brown, B. B. (1981). Pharmacokinetics of high and low dose alfentanil. *Anesthesiology*, **55**, A256.

Bovill, J. G., Sebel, P. S., Blackburn, C. L., and Heykants, J. (1981). Kinetics of alfentanil and sufentail: A comparison. *Anesthesiology*, **55**, A174.

De Lange, S., De Bruijn, N., Stanley, T. H., and Boscoe, M. J. (1981). Alfentanil–oxygen anesthesia: Comparison of continuous infusion and frequent bolus techniques for coronary artery surgery. *Anesthesiology*, **55**, A42.

——Stanley, T. H., and Boscoe, M. J. (1981). Alfentanil–oxygen anaesthesia for coronary artery surgery. *Br. J. Anaesth.*, **53**, 1291.

————De Bruijn, N., Philbin, D. M., and Coggins, C. H. (1981). Antidiuretic hormone responses during coronary artery surgery with sufentanil–oxygen and alfentanil–oxygen anesthesia in man. *Anesthesiology*, **55**, A47.

Kay, B., and Pleuvry, B. (1980). Human volunteer studies of alfentanil (R 39209), a new short-acting narcotic analgesic. *Anaesthesia*, **35**, 952.

——Stephenson, D. K. (1980). Alfentanil (R 39209): Initial clinical experience with a new narcotic analgesic. *Anaesthesia*, **35**, 1191.

Lowenstein, E., and Philbin, D. M. (1981). Narcotic "anesthesia" in the eighties. *Anesthesiology*, **55**, 195.

McClain, D. A., and Hug, C. C. (1980). Intravenous fentanyl kinetics. *Clin. Pharmacol. Ther.*, **28**, 106.

Nauta, J., De Lange, S., Koopman, D., Spierdijk, J., and Stanley, T. H. (1981). Anesthetic induction with alfentanil: Comparison with thiopental, midazolam and etomidate. *Anesthesiology*, **55**, 255.

Neimegeers, C. J. E., and Janssen, P. A. J. (1981). Alfentanil (R 39209)—A particularly short-acting intravenous narcotic analgesic in rats. *Drug Devel. Res.*, **1**, 83.

Sebel, P. S., and Bovill, J. G. (1982). Cardiovascular effects of sufentanil anesthesia. *Anesth. Analg.* (*Cleve.*), **61**, 115.

————Boekhorst, R. A. A., and Rog, P. (1982a). Cardiovascular effects of high-dose fentanyl: A study in patients undergoing cardiac surgery. *Acta Anaesthesiol. Scand.*, **26**, 308.

————Fiolet, J., Touber, J. L., and Philbin, D. M. (1982b). Hormonal responses to sufentanil anesthesia. *Anesth. Analg.* (*Cleve.*), **61**, 214.

————Schellekens, A. P. M., and Hawker, C. D. (1981). Hormonal responses to high-dose fentanyl anaesthesia: A study in patients undergoing cardiac surgery. *Br. J. Anaesth.*, **53**, 941.

Smith, N. T., Wesseling, K. H., Weber, J. A. P., and De Wit, B. (1974). Preliminary evaluation of a pulse contour cardiac output computer in man: Feasibility of brachial or radial artery pressures. *Proc. San Diego Biomed. Symp.*, **13**, 113.

Spierdijk, J., Van Kleef, J., Nauta, J., Stanley, T. H., and De Lange, S. (1980). Alfentanil—a new narcotic induction agent. *Anesthesiology*, **53**, S32.

Stanley, T. H., Berman, L., Green, O., and Robertson, D. (1980). Plasma catecholamine and cortisol responses to fentanyl–oxygen anesthesia for coronary artery operations. *Anesthesiology*, **53**, 250.

Stanley, T. H., Philbin, D. M., and Coggins, C. H. (1979). Fentanyl–oxygen anaesthesia for coronary artery surgery: Cardiovascular and antidiuretic hormone responses. *Can. Anaesth. Soc. J.*, **26**, 168.

——Webster, L. R. (1978). Anesthetic requirements and cardiovascular effects of fentanyl–oxygen and fentanyl–diazepam–oxygen anesthesia in man. *Anesth. Analg.* (*Cleve.*), **57**, 411.

Thomas, B. (1978). Monitoring of cardiac output by pulse contour method. *Acta Anaesthesiol. Belg.*, **29**, 259.

Van Leeuwen, L., and Deen, L. (1981). Alfentanil, a new, potent and very short-acting morphinomemetic for minor operative procedures. *Anaesthesist*, **30**, 115.

————Helmers, J. H. (1981). A comparison of alfentanil and fentanyl in short operations with special reference to their duration of action and postoperative respiratory depression. *Anaesthesist*, **30**, 397.

Wallenstein, S., Zucker, C. L., and Fleiss, J. L. (1980). Some statistical methods useful in circulation research. *Circ. Res.*, **47**, 1.

Waller, J. L., Hug, C. C., Nagle, D. M., and Craver, J. M. (1981). Hemodynamic changes during fentanyl–oxygen anesthesia for aorto–coronary bypass operation. *Anesthesiology*, **55**, 212.

Wesseling, K. H., Purschke, R., Smith, N. T., Wust, H. J., De Wit, B., and Weber, H. A. P. (1976). A computer module for the continuous monitoring of cardiac output in the operating theatre and ICU. *Acta Anaesthesiol. Belg.*, **27**, 327.

——Smith, N. T., Nichols, W. W., Weber, H., De Wit, B., and Beneken, J. E. W. (1974). Beat to beat cardiac output from the arterial pressure contour; in *Measurement of Anaesthesia* (eds S. A. Feldman, J. M. Leigh and J. Spierdijk), p. 150. Leiden: Leiden University Press.

## EFFETS CARDCOVASCULAIRES D'UNE ANESTHESIE A L'ALFENTANIL

### RESUME

Chez 30 patients subissant une chirurgie cardiaque, l'anesthésie a été induite par l'alfentanil $125\,\mu g\,kg^{-1}$ et entretenue par une perfusion d'alfentanil $0{,}5\,mg\,kg^{-1}\,h^{-1}$ jusqu'au démarrage de la CEC, puis alfentanil, $0{,}25\,mg\,kg^{-1}\,h^{-1}$ ensuite jusqu'à la fin de l'acte chirurgical. Du pancuronium était administré et les poumons étaient ventilés par un mélange d'air et d'oxygène. Chez la majorité des patients, il n'y a pas eu de modifications significatives des paramètres hémodynamiques tout au long de l'étude, bien que deux sujets aient reçu du nitroprussiate pour contrôler une hypertension et que chez un sujet l'hypertension ait été si sévère que cette technique d'anesthésie a dû être abandonnée. Une hypotension transitoire est survenue à l'induction chez un patient. Vingt-six patients ont eu besoin de doses supplémentaires d'alfentanil avant la CEC. Ces résultats montrent que l'anesthésie par une perfusion d'alfentanil procure une stabilité cardiovasculaire satisfaisante pour la chirurgie cardiaque.

## KARDIOVASKULÄRE WIRKUNGEN DER NARKOSE MIT ALFENTANIL

### ZUSAMMENFASSUNG

Bei 30 Patienten, die sich einer Herzoperation unterziehen mußten, wurde die Narkose mit Alfentanil $125\,\mu g\,kg^{-1}$ eingeleitet und mit einer Infusion mit Alfentanil $0,5\,mg\,kg^{-1}\,h^{-1}$ bis zum Beginn des kardiopulmonalen Bypass aufrechterhalten, und danach Alfentanil $0,25\,mg\,kg^{-1}\,h^{-1}$ bis zum Ende der Operation gegeben. Es wurde mit Pancuronium relaxiert und die Lunge mit Sauerstoff-Luft-gemisch beatmet. Bei der Mehrzahl der Patienten gab es keine signifikanten Veränderungen der kardiovaskulären Parameter während der Untersuchung, obwohl zwei Patienten Natriumnitroprussid zur Behandlung eines Hochdrucks erhielten und bei einem Patienten der Hochdruck so ernst war, daß diese Narkoseform aufgegeben wurde. Vorübergehende Hypotension zeigte sich bei einem Patienten bei der Einleitung. Sechsundzwanzig Patienten brauchten eine zusätzliche Gabe von Alfentanil vor dem Bypass. Diese Ergebnisse zeigen, daß die Narkose mit Alfentanil Infusion eine für eine Herzoperation ausreichende Stabilität des Herz-Kreislaufsystems besitzt.

## EFECTOS CARDIOVASCULARES DE LA ANESTESIA CON ALFENTANILO

### SUMARIO

Se indujo anestesia con $125\,\mu g\,kg^{-1}$ de alfentanilo en 30 pacientes sometidos a intervención quirúrjica cardiaca, manteniéndose dicha anestesia con una infusión de $0,5\,mg\,kg^{-1}\,h^{-1}$ de alfentanilo hasta el comienzo de la desviación cardiopulmonar y con $0,25\,mg\,kg^{-1}\,h^{-1}$ posteriormente hasta el término de la intervención quirúrjica. Se administró pancuronio y se ventilaron los pulmones con aire en oxígeno. En la mayoría de los pacientes no hubo cambios significativos en las mediciones cardiovasculares efectuadas a lo largo del estudio, aunque dos de los pacientes recibieron nitroprusiato de sodio para controlar la hipertensión y en uno de los pacientes la hipertensión fue tan intensa que este método de anestesia se desechó. En uno de los pacientes se produjo hipotensión momentánea durante la inducción. Veintiseis de los pacientes necesitaron alfentanilo suplementario antes de la desviación. Estos resultados indican que la anestesia mediante una infusión de alfetanilo provee la estabilidad cardiovascular necesaria para la intervención quirúrjica del corazón.

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# I.V. LABETALOL IN THE TREATMENT OF HYPERTENSION FOLLOWING CORONARY-ARTERY SURGERY

D. R. MOREL, A. FORSTER AND P. M. SUTER

## SUMMARY

The cardiovascular effects of incremental fixed i.v. doses of labetalol were evaluated in 10 normovolaemic sedated patients presenting with hypertension and tachycardia in the early period after myocardial revascularization. A first dose of 20 mg was sufficient to provoke a significant ($P < 0.01$) mean decrease in systolic (−9.3%), diastolic (−8.2%) and mean arterial (−7.9%) pressure (AP) and in the rate–pressure product (RPP) (−13.1%). The mean heart rate (HR) did not change significantly, but a linear correlation could be established between the change at 2 min and the value before injection ($r = 0.73$). A second dose of labetalol 40 mg given 5 min later did not decrease AP further, but a significant decrease in HR was noted. A marked difference in the individual response among patients was found as the range of effective total doses per kg body weight was 0.6–4.1 mg kg$^{-1}$ (mean 2.2). Apart from one patient, no patient needed vagolytic or sympathomimetic drugs to oppose the alpha or beta actions of labetalol during the 24-h follow-up period.

The occurrence of hypertension and tachycardia after myocardial revascularization has been observed in 30–60% of patients undergoing coronary artery surgery (Estafanous et al., 1973; Hoar, Hickey and Ullyot, 1976; Roberts et al., 1977; Fouad, Estafanous and Tarazi, 1978). This syndrome appears usually within the first 2 h after the patient has returned to the intensive care unit (ICU) and lasts about 4–8 h. It can lead to various and severe complications, including haemorrhage, arrhythmia, myocardial ischaemia or infarction. Several treatments have been proposed, including vasodilator therapy (Estafanous et al., 1973; Roberts et al., 1977; Fouad, Estafanous and Tarazi, 1978), extradural anaesthesia (Hoar, Hickey and Ullyot, 1976), preoperative stellate ganglion blockade (Bidwai et al., 1979). Beta-adrenergic blocking agents seem less successful; i.v. propranolol was shown to increase total peripheral resistance, partly in response to the reduction of cardiac output and also possibly because of unopposed alpha stimulation (Ulrych et al., 1968).

Labetalol is a drug which competitively blocks both alpha- and beta-adrenoceptors (Farmer et al., 1972; Brittain and Levy, 1976), and which has an elimination plasma half-life of 4.0 ± 0.5 h in man (Martin, Hopkins and Bland, 1976). It has the advantage over pure vasodilators of counteracting the baroreceptor reflex increase in HR and cardiac output elicited by the AP decrease. On the other hand, its alpha-adrenoceptor blocking property decreases left ventricular filling pressure, which can be increased by the use of pure beta-adrenoceptor antagonists (Peter et al., 1978). These unique pharmacological properties make labetalol particularly attractive as an antihypertensive agent, especially in patients suffering from coronary artery disease in whom the aim is to reduce myocardial oxygen consumption. As the latter can be estimated from the rate–pressure product (RPP) (Gobel et al., 1978), labetalol, acting on both components of this product, will improve angina pectoris by diminishing myocardial oxygen consumption.

The purpose of this study was to evaluate the cardiovascular effects of incremental fixed i.v. doses of labetalol in patients presenting with hypertension and tachycardia in the early period following myocardial revascularization.

## PATIENTS AND METHODS

The study was approved by the Committee on Human Research of our institution.

### *Patients*

The study was begun in the ICU, during the first 2 h after operation in 10 patients who presented with hypertension and tachycardia, as defined below,

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TABLE I. *Patients studied and haemodynamic data before operation (n = 10). AP = arterial pressure; RPP = rate–pressure product; LVEDP = Left ventricular end-diastolic pressure (catheterism laboratory data)*

| | Mean ± SD | Range |
|---|---|---|
| Age (yr) | 57 ± 9 | 45–71 |
| Weight (kg) | 81 ± 9 | 69–95 |
| Systolic AP (kPa) | 20 ± 3 | 18–25 |
| Diastolic AP (kPa) | 12 ± 1.6 | 11–15 |
| Heart rate (beat $\text{min}^{-1}$) | 72 ± 8 | 55–80 |
| RPP (kPa $\text{min}^{-1}$) | 1423 ± 200 | 1100–1727 |
| LVEDP (kPa) | 2.5 ± 0.8 | 1.6–3.7 |
| Ejection fraction (%) | 57 ± 12 | 30–70 |

after an elective aortocoronary bypass operation. The clinical data are reported in table I. All patients were males and coronary artery disease had been recognized clinically and confirmed before operation with coronary arteriography. All but one patient were receiving adequate beta-blocker treatment (oxprenolol or pindolol), but did not receive a beta-blocker the day of surgery, and three patients were known to be hypertensive before operation.

### *Anaesthesia and postoperative management*

The anaesthetic technique and the postoperative management were identical in all patients. Anaesthesia was induced with flunitrazepam 0.03 mg $\text{kg}^{-1}$ and pancuronium bromide 0.1 mg $\text{kg}^{-1}$ and maintained with 40% oxygen in 60% nitrous oxide and fentanyl (total dose 1.0–1.5 mg) and droperidol 10–15 mg. Recovery from cardiopulmonary bypass was achieved without difficulty in all patients and no vasopressor agent was used after coronary bypass.

The tracheal tube was kept in place and the lungs artificially ventilated for the first 12 h after operation to maintain arterial $P\mathrm{CO}_2$ between 4.6–5.3 kPa and arterial $P\mathrm{O}_2$ greater than 16 kPa. The electrocardiogram and AP were monitored continuously. Central venous pressure (c.v.p.), urine output and blood loss from the chest drains were recorded and all losses adequately replaced. Serum electrolytes and haematocrit were measured regularly and any abnormality corrected. The patients were sedated with small doses of morphine (mean dose ± SD) 5.3 ± 2.8 mg, diazepam 8.5 ± 5.2 mg and chlorpromazine 5.0 ± 2.6 mg i.v. over the first 4 h after operation.

A hypertension and tachycardia syndrome was defined as a sustained increase of RPP of more than 665 kPa $\text{min}^{-1}$ greater than the patient's preoperative value, which ranged between 1100 and 1720, with systolic AP remaining greater than 16 kPa, excluding hypoxia, hypercarbia, shivering, fighting the ventilator or intolerance of the endotracheal tube, and which could not be reversed with simple sedation. The patients were admitted to the labetalol study if they maintained a hypertension and tachycardia syndrome for at least 30 min in spite of proper sedation and analgesia, as judged clinically.

Once the patient was in the study, the following variables were measured and recorded continuously on a four-channel polygraph: e.c.g. and HR by precordial derivation, systolic, diastolic and mean arterial pressure through a radial artery catheter and c.v.p. through a venous catheter with the zero reference point situated at mid-axillary level. RPP was calculated from the product of systolic AP × HR. The recording of the data was continued for 30 min, then the haemodynamic variables were noted every hour for a 24-h follow-up period. Secondary effects of labetalol and the need for vasoactive drugs were also recorded.

Labetalol was administered i.v. through a vein in the forearm over 15 s. First all patients were given a 20-mg dose. After 5 min, 40 mg was injected if hypertension and tachycardia were still present. Five minutes later, the patients who were still presenting with the syndrome received 80 mg of labetalol and this dose again every 5 min if indicated, until a total dose of labetalol 300 mg was achieved.

### *Statistical analyses*

A Student's paired *t* test was used for statistical evaluation. The results are presented as means ± one standard deviation of the mean ($\bar{x}$ ± SD).

## RESULTS

The time courses of changes in arterial pressure, HR and the RPP are reported in figure 1. The first dose of labetalol 20 mg was sufficient to provoke a significant ($P < 0.01$) mean decrease in systolic (−9.3%), diastolic (−8.2%) and mean arterial (−7.9%) pressure and in RPP (−13.1%). Mean HR did not change significantly, but a linear correlation could be established between change at 2 min and the value before injection (fig. 2; $r = -0.73$). A similar correlation could be established between the change in systolic AP after 1 min and the value before injection: $r = -0.62$, $P < 0.05$ (fig. 3).

The second dose of labetolol given 5 min later did not decrease AP further, but a significant decrease in HR was noted. Eight of 10 patients required a

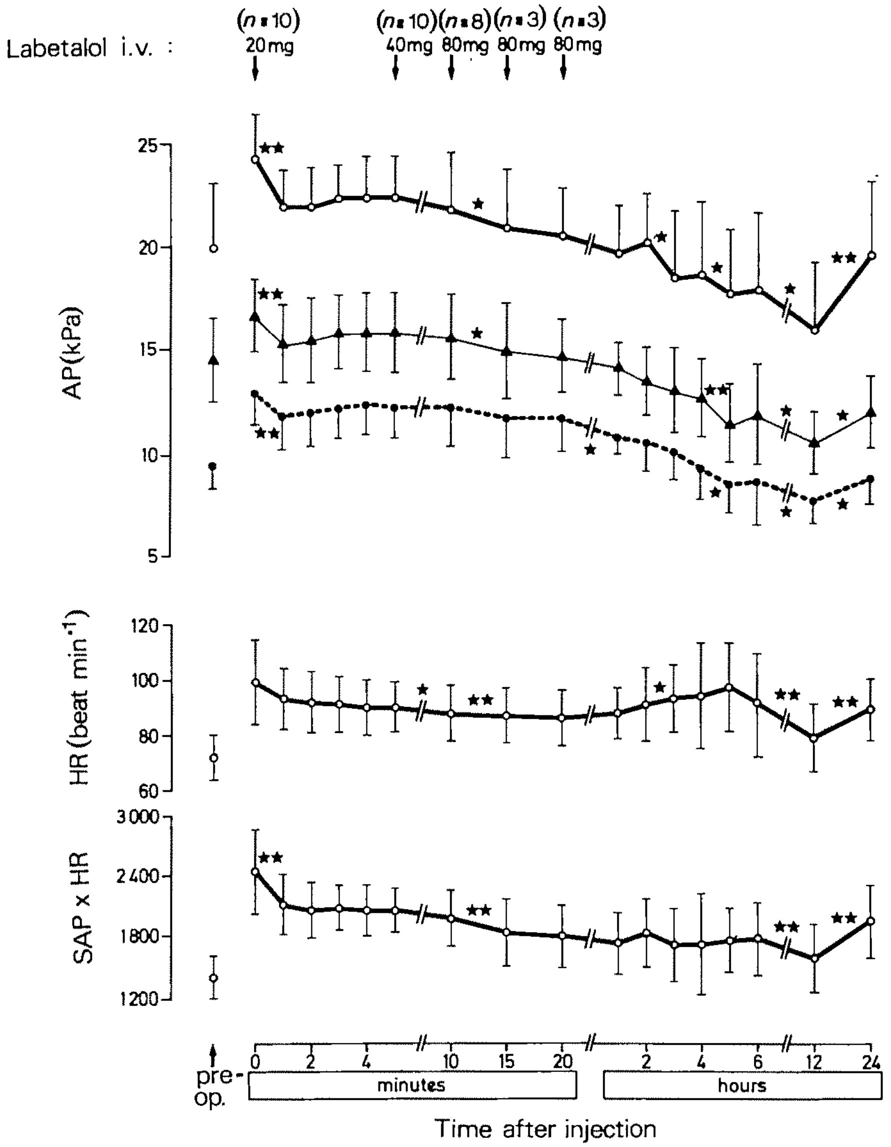

FIG. 1. Haemodynamic effects of labetalol (mean ± SD, $n = 10$) given by incremental i.v. bolus injection. $*P<0.05$; $**P<0.01$. Arterial pressures: ○ = systolic, ▲ = mean, ● = diastolic.

third injection at 10 min and its haemodynamic effect was statistically significant. Three patients continued to manifest the hypertension and tachycardia syndrome after a total dose of 140 mg, but responded after two additional doses, each of 80 mg of labetalol. Thus there was a marked difference in the individual response among patients: the range of total doses per kg body weight was 0.6–4.1 mg kg$^{-1}$ (mean 2.2) and there was no correlation between the need for labetalol and clinical and haemodynamic data before operation.

If the three "resistant" patients, who needed up to 300 mg of labetalol to attenuate their hypertension and tachycardia syndrome were excluded from the study, then the remainder, who received a mean dose of labetalol 1.46 ± 0.56 mg kg$^{-1}$, had a signific-

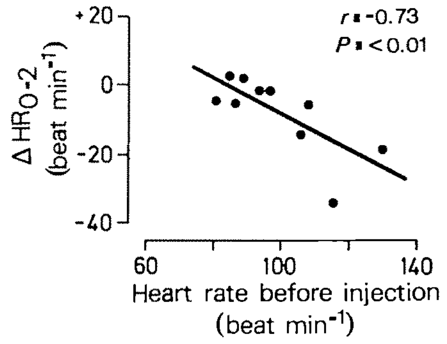

FIG. 2. Linear correlation between the decrease in heart rate during the first 2 min ($\Delta$ HR$_{0-2}$) after labetalol injection and its control value.

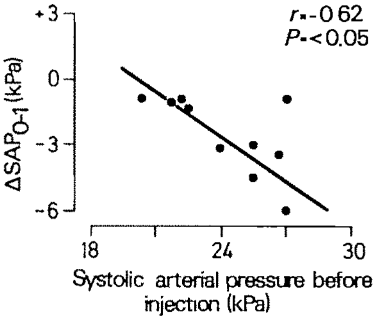

FIG. 3. Linear correlation between the decrease in systolic arterial pressure during the 1st min ($\Delta$ SAP$_{0-1}$) after labetalol injection and its control value.

ant ($P<0.005$) percentage decrease in their haemodynamic variables of 11% (systolic), 10% (diastolic), 10% (mean AP) and 18% (RPP). In these patients, the correlation between the change in systolic AP after 1 min *v.* the value before injection was $r=0.91$ ($P<0.005$).

During the following hours AP continued to decrease spontaneously, even to values less than those before operation, with a smallest value almost always at 12 h after the start of the study, at which time the HR was also slowest. Twenty-four hours after the beginning of the investigation, AP values were about the same as those occurring before operation, while there persisted a relative faster HR (89 beat min$^{-1}$).

During the whole period of investigation, c.v.p. remained stable, with a mean value of 7 ± 4 cm $H_2O$ before injection and ranging from 7 ± 4 to 10 ± 3 cm $H_2O$ after labetalol. Rectal temperature at the beginning of the study was 36 ± 0.4 °C and regularly increased to 38.5 ± 0.3 °C 6 h later and to 38.1 ± 0.3 °C at 24 h.

Apart from the haemodynamic changes produced by labetalol, we observed a reduction of ventricular extrasystolic beats in three patients. In one patient, unifocal ectopic ventricular beats appeared after the first 80-mg dose, lasting for 15 min. Another patient, the oldest of the group (71 yr), and who had the greatest left ventricular end-diastolic pressure value before operation (3.7 kPa) and the worst ejection fraction (30%), suddenly presented multifocal ventricular ectopic beats followed by bradycardia and ventricular fibrillation 90 min after the injection. After internal cardiac massage and defibrillation, the patient's heart recovered sinus rhythm for 30 min, then a similar episode occurred again and cardiopulmonary resuscitation was unsuccessful. The postmortem examination of the heart showed a large fresh anterior infarct.

Apart from this patient, no subject needed vagolytic or sympathomimetic drugs to oppose the alpha or beta actions of labetalol during the 24-h follow-up period, but three patients received small doses of dopamine (3-4 µg kg$^{-1}$ min$^{-1}$) to improve renal perfusion between 6 and 18 h after operation.

## DISCUSSION

Hypertension after myocardial revascularization with or without tachycardia in well ventilated and sedated patients is mainly caused by sympathetic hyperactivity with increased peripheral vascular resistance associated with increased plasma catecholamine concentrations (Roberts et al., 1977). In our institution, the frequency of this syndrome, as defined in this study, is 45% of 120 coronary bypass operations per year, which is in accordance with previous reports (Estafanous et al., 1973; Hoar, Hickey and Ullyot, 1976; Roberts et al., 1977; Fouad, Estafanous and Tarazi, 1978).

The theoretical advantage of labetalol in antagonizing simultaneously both alpha- and beta-adrenoceptor sites has been confirmed in our study. Labetalol 20 mg i.v. administered over 15 s has proved to be efficient in diminishing RPP clinically and statistically. The second (40 mg) and the third doses (80 mg) produced further progressive reductions of RPP. Three of 10 subjects, none hypertensive before operation, did not react to the loading dose of 140 mg and needed up to 300 mg to decrease RPP adequately.

An interesting feature of labetalol is the fact that individual changes are influenced by the degree of resting sympathetic drive, thus more marked reductions in HR have been observed in patients with high HR values before injection, just as a greater decrease in systolic AP is found with high AP values before injection.

Our starting doses (20 mg) were far less than the dose recommended for chronically hypertensive subjects (Pearson and Havard, 1976; Cumming et al., 1979), but larger than those administered by Meretoja and others (1980) to a similar group of patients (mean total dose 15 mg). This difference in the sensitivity of such patients may be explained by the different times after the end of operation at which labetalol was given. Meretoja administered the drug, on average, 6 h after the end of extracorporeal circulation, a time at which the post-myocardial revascularization hypertension syndrome is frequently ceasing spontaneously, whatever treatment is applied. The AP of Meretoja's patients were significantly lower (mean 13.3 kPa) with one patient having a mean AP of 10 kPa associated with HR 59 beat min$^{-1}$ before the labetalol injection. The difference between his and our findings is therefore not surprising: the earlier patients needed less adrenergic antagonists than those reported in the present study, in which labetalol was injected after operation during the first 2 h in more severely hypertensive patients.

The relative long duration of action of labetalol, lasting for 4–18 h (Pearson and Havard, 1976; Cumming et al., 1979), may be helpful in protecting the patient with coronary artery disease during the hypertensive period, but its use implies a careful monitoring of blood volume because physiological compensatory mechanisms may be attenuated by labetalol. It is difficult to determine if the fatal outcome in one patient in our series was precipitated by the use of labetalol, but it is noteworthy that this patient had a previous history of recurrent episodes of supraventricular tachycardia necessitating electrical shock and that he was the only patient not receiving beta-blockade treatment. Although Chiarello and others (1980) have demonstrated a protective effect of labetalol on myocardial cell necrosis after coronary artery occlusion in rats and studies in humans emphasized the beneficial effect of this drug in patients with angina pectoris (Besterman and Spencer, 1979) or acute myocardial infarction with systemic hypertension (Marx and Reid, 1979), once the arrhythmia in this patient had occurred, it was probably more difficult to perform successful cardiac resuscitation under labetalol than under a short-acting vasodilating agent. Thus, if the hypertension cannot be corrected by an i.v. dose of labetalol 100–150 mg administered over 10 min, then another mode of decreasing AP, for instance by i.v. sodium nitroprusside, should be considered.

We conclude that i.v. labetalol administered over 15 s in incremental fixed doses starting with 20 mg and, if necessary, doubling the dose after a 5-min interval until a total dose of 2 mg kg$^{-1}$ is achieved, is safe and effective in producing a rapid reduction in RPP in patients presenting an acute postmyocardial revascularization hypertension syndrome. It would seem from our study that, if there is no effect after a 140-mg loading dose, greater doses of labetalol have little further beneficial action and can mask a slowly developing cardiovascular decompensation or may decrease the efficiency of a haemodynamic resuscitation.

## REFERENCES

Besterman, E. M. M., and Spencer, M. (1979). Open evaluation of labetalol in the treatment of angina pectoris occurring in hypertensive patients. *Br. J. Clin. Pharmacol.*, 8, (Suppl.), 205S.

Bidwai, A. V., Rogers, C. R., Pearce, M., and Stanley, T. H. (1979). Preoperative stellate-ganglion blockade to prevent hypertension following coronary-artery operations. *Anesthesiology*, 51, 345.

Brittain, R. T., and Levy, G. P. (1976). A review of the animal pharmacology of AH 5158: a drug which blocks both alpha and beta adrenoceptors. *Br. J. Clin. Pharmacol.*, 3, (Suppl.), 681S.

Chiarello, M., Brevetti, G., De Rosa, G., Acunzo, R., Petillo, F., Rengo, F., and Condorelli, M. (1980). Protective effects of simultaneous alpha and beta adrenergic receptor blockade on myocardial cell necrosis after coronary arterial occlusion in rats. *Am. J. Cardiol.*, 46, 249.

Cumming, A. M. A., Brown, J. J., Lever, A. F., Mackay, A., and Robertson, J. I. S. (1979). Treatment of severe hypertension by repeated bolus injection of labetalol. *Br. J. Clin. Pharmacol.*, 8, (Suppl.), 199S.

Estafanous, F. G., Tarazi, R. C., Viljoen, J. F., and El Tawil, M. Y. (1973). Systemic hypertension following myocardial revascularization. *Am. Heart J.*, 85, 732.

Farmer, J. B., Kennedy, I., Levy, G. P., and Marshall, R. J. (1972). Pharmacology of AH 5158: a drug which blocks both alpha and beta adrenoceptors. *Br. J. Pharmacol.*, 45, 660.

Fouad, F. M., Estafanous, F. G., and Tarazi, R. C. (1978). Hemodynamics of postmyocardial revascularization hypertension. *Am. J. Cardiol.*, 41, 564.

Gobel, F. L., Nordstrom, L. A., Nelson, R. R., Jorgensen, C. R., and Wang, Y. (1978). The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. *Circulation*, 57, 549.

Hoar, P. F., Hickey, R. F., and Ullyot, D. G. (1976). Systemic hypertension following myocardial revascularization. A method for treatment using epidural anesthesia. *J. Thorac. Cardiovasc. Surg.*, 71, 859.

Martin, L. E., Hopkins, R., and Bland, R. (1976). Metabolism of labetalol by animals and man. *Br. J. Clin. Pharmacol.*, 3, (Suppl.), 695S.

Marx, P. G., and Reid, D. S. (1979). Labetalol infusion in acute myocardial infarction, with systemic hypertension. *Br. J. Clin. Pharmacol.*, 8, (Suppl.), 233S.

Meretoja, O. A., Allonen, H., Arola, M., and Laaksonen, V. O. (1980). Combined alpha- and beta-blockade with labetalol in post-open heart surgery hypertension. *Chest*, 6, 810.

Pearson, R. M., and Havard, C. W. H. (1976). Intravenous labetalol in hypertensive patients treated with beta-adrenoceptor-blocking drugs. *Br. J. Clin. Pharmacol.*, 3, (Suppl.), 795S.

Peter, T., Norris, R. M., Clarke, E. D., Heng, M. K., Singh, B. N., Williams, B., Howell, D. R., and Ambler, P. K. (1978). Reduction of enzymes levels by propranolol after acute myocardial infarction. *Circulation*, 57, 1091.

Roberts, A. J., Niarchos, A. P., Subramanian, V. A., Abel, R. M., Herman, S. D., Sealey, J. E., Case, D. B., White, R. P., Johnson, G. A., Laragh, J. H., and Gay, W. A. jr (1977). Systemic hypertension associated with coronary artery bypass surgery. *J. Thorac. Cardiovasc. Surg.*, 74, 846.

Ulrych, M., Frohlich, E. D., Dustan, H. P., and Page, I. H. (1968). Immediate hemodynamic effects of beta-adrenergic blockade with propanolol in normotensive and hypertensive man. *Circulation*, 37, 411.

## I.V. LABETALOL ZUR BEHANDLUNG DES HYPERTONUS NACH OPERATION AN DEN KORONARARTERIEN

### ZUSAMMENFASSUNG

Die kardiovaskulären Wirkungen von Labetabol in einer festgelegten ansteigenden i.v. Dosierung wurden an zehn normovolämischen, sedierten Patienten gemessen, die in der frühen postoperativen Phase nach der myokardialen Revaskularisierung an Hypertonus und Tachykardie litten. Eine erste Dosis von 20 mg reichte aus, um eine signifikante durchschnittliche Senkung des systolischen (−9,3%), des diastolischen (−8,2%) und des mittleren arteriellen Druckes sowie des Produktes aus Frequenz und Druck (RRP) hervorzurufen (−13,1%). Die mittlere Herzfrequenz änderte sich nicht signifikant, aber es konnte eine lineare Korrelation hergestellt werden zwischen der Veränderung nach 2 min und dem Wert vor der Injektion ($r = 0{,}73$). Eine 2. Dosis von Labetalol (40 mg), die 5 min später verabreicht wurde, senkte den AD nicht weiter, aber es war ein signifikanter Abfall der HF festzustellen. In der individuellen Ansprechbarkeit bestand ein großer Unterschied zwischen den Patienten, da der Bereich der wirksamen Gesamtdosen pro kg KM von 0,6 bis 4,1 $\text{mg kg}^{-1}$ (durchschnittlich 2,2) reichte. Ausser einem Patienten benötigte keiner vagolytische oder sympathomimetische Medikamente, um Wirkungen auf alpha- oder beta-Rezeptoren von Labetolol in den darauffolgenden 24 h entgegenzuwirken.

## LE LABETALOL I.V. DANS LE TRAITEMENT DE L'HYPERTENSION APRES CHIRURGIE DES ARTERES CORONAIRES

### RESUME

Les effets cardiovasculaires de doses croissantes prédéterminées de labétalol ont été étudies chez 10 patients normovolémiques ayant reçu des sédatifs et présentant une hypertension et une tachycardie dans la période post-opératoire précoce après une revascularisation du myocarde. Une première dose de 20 mg était suffisante pour induire une diminution moyenne significative ($P < 0{,}01$) des pressions artérielles systoliques (−9,3%), diastolique (−8,2%) et moyenne (−7,9%) et du produit pression fréquence (PPF) (−13,1%). La fréquence cardiaque moyenne (FC) n'était pas significativement modifiée mais une corrélation linéaire pouvait être établie entre les modifications à 2 min et la valeur avant l'injection ($r = 0{,}73$). Une deuxième dose de labétalol (40 mg) administrée 5 min plus tard n'entraînait pas de diminution significative de la FC. La réponse individuelle variait beaucoup selon les patients et la gamme de doses totales efficaces park kg de poids corporel allait de 0,6 à 4,1 $\text{mg kg}^{-1}$ (moyenne 2,2). A l'exception d'un patient, aucun sujet n'a eu besoin de vagolytiques ou de sympathomimétiques pour antagoniser les actions alpha ou beta de labétalol pendant les 24 h de la période d'étude.

## LABETALOL I.M. EN EL TRATAMIENTO DE LA HIPERTENSIÓN DESPUES DE CIRUJÍA DE LA ARTERIA CORONARIA

### SUMARIO

Se procedió a la evaluación de los efectos cardiovasculares de dosis i.v. crecientes fijas de labetalol administradas a 10 pacientes normovolémicos reposados que padecían de hipertensión y taquicardia en el periodo inmediato después de una revascularización miocárdiaca. Bastó con una primera dosis de 20 mg para provocar un descenso medio significante ($P < 0{,}01$) de la presión (AP) arterial media (−7,9%), sistólica (−9,3%) y diastólica (−8,2%) así como el producto presión–ritmo (RPP) (−13,1%). El ritmo cárdiaco medio (HR) no cambió de manera significante, pero pudo establecerse una correlación linear entre el cambio a los 2 min y el valor antes de la inyección ($r = 0{,}73$). Una segunda dosis de labetalol de 40 mg administrada 5 min después no hizo bajar más la AP, pero se observó una disminución significativa del HR. Se notó una diferencia marcada en la respuesta individual entre los pacientes según variaba la gama de dosis totales efectivas por kg de peso corporal de 0,6 a 4,1 $\text{mg kg}^{-1}$ (promedio 2,2). Salvo un solo paciente, ningún otro necesitó substancias vagolíticas o simpatomiméticas que se opusieran a las acciones alfa o beta del labetalol durante el periodo siguiente de 24 h.

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# EFFECT OF SODIUM NITROPRUSSIDE-INDUCED HYPOTENSION ON PULMONARY DEADSPACE

H. J. KHAMBATTA, J. G. STONE AND R. S. MATTEO

SUMMARY

Deliberate hypotension with nitroprusside produced a 40% reduction in mean arterial pressure, but it did not cause any change in the pulmonary deadspace to tidal volume ratio ($V_D/V_T$). This was achieved by adequate hydration both before and during hypotension, as indicated by constant filling pressures. Thus we have shown that deliberate hypotension *per se* does not increase $V_D/V_T$, and that vasodilatation may bring about a relatively hypovolaemic state and be responsible for the increase in $V_D/V_T$ observed by previous workers.

Deliberate hypotension induced by ganglionic blockers was reported to produce an increase in pulmonary deadspace (Eckenhoff et al., 1963), and this led the authors to recommend the use of a high inspired oxygen concentration during anaesthesia with induced hypotension. In the most recent edition of the textbook *General Anaesthesia* (Gray, Nunn and Utting, 1980), this recommendation still holds, but no one has studied pulmonary deadspace ventilation during hypotensive anaesthesia using current vasodilating drugs. The question whether induced hypotension itself is responsible for the increase in pulmonary deadspace has not been answered. This is the subject of the present study.

## METHOD

Ten patients (six male), average age 30 yr (range 23–44 yr), were studied with their informed consent and approval by the Institutional Review Board for human subjects. All patients underwent lumbar laminectomy to remove degenerated herniated disc material and spinal fusion with autogenous iliac bone graft. Preoperative history, physical and laboratory examination revealed no medical problems except those related to their forthcoming surgery.

Premedication consisted of oral diazepam 10 mg the night before surgery and i.m. atropine 0.5 mg and quinalbarbitone 100 mg 1 h before induction of anaesthesia. Anaesthesia was induced with thiopentone 250–300 mg i.v. and the trachea was intubated after muscle relaxation with suxamethonium 100 mg. Anaesthesia was maintained with 1.2% halothane in oxygen. Muscle relaxation was re-established with tubocurarine 0.6 mg kg$^{-1}$. The lungs were mechanically ventilated with an Air Shields Ventimeter ventilator at a constant minute ventilation and a constant inspired gas mixture throughout the entire procedure. The ratio of inspiration to expiration was 1 : 3. Tidal volume was set at 10 ml kg$^{-1}$ and the rate was adjusted to keep $Pa_{CO_2}$ in the range 4–4.5 kPa. All measurements were made with the patients in the prone position. The head and torso were at the same level. The arms were outstretched and in front. The patients were supported with well-padded bolsters with the abdomen free.

A 20-gauge Teflon catheter was placed in the radial artery and a 5F balloon-tipped catheter was floated into a pulmonary artery through an arm vein for the recording of pressures and the collection of blood samples. Pressure recordings were made using a Hewlett–Packard monitoring system. Transducers were zeroed at the heart level.

Measurements, which included mean arterial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac output, arterial carbon dioxide tension ($Pa_{CO_2}$) and mixed expired carbon dioxide tension ($P\bar{E}_{CO_2}$), were made after steady-state periods of at least 60 min. Measurements were made: during anaesthesia and surgery (control); during deliberately induced hypotension with nitroprusside (hypotension); after nitroprusside had been discontinued and arterial pressure had returned to the control value (recovery). Blood samples for blood-gas analysis were collected in heparinized glass syringes and analysed immediately in duplicate using an Instrumentation

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Laboratories 313 blood-gas analyser. Cardiac output was measured by the dye-dilution technique using indocyanine green and a Beckman Cardiodensitometer. Mixed expired gas samples were collected in a 30-litre Douglas bag using a non-rebreathing one-way valve system. Mixed expired carbon dioxide tension was measured in triplicate by an Instrumentation Laboratories 313 gas analyser which was calibrated with three known carbon dioxide standards to obtain a three-point line.

Hypotension was induced with an i.v. infusion of 0.04% sodium nitroprusside. The infusion rate was regulated with a Holter infusion pump to achieve a 40% reduction in mean arterial pressure from the control value. During the operation these patients received an average of 500 ml of 5% dextrose in water and 2500 ml of Ringer's lactate solution. Of this total of 3 litres of fluid, 2 litres was given before induction of hypotension. Blood loss during surgery was estimated to be less than 500 ml. The average duration of the whole procedure was 3.5 h and the period of hypotension was 80 min.

Pulmonary deadspace to tidal volume ratio ($V_D/V_T$) was calculated using the standard formula:

$$V_D/V_T = \frac{Pa_{CO_2} - P_{E}{}_{CO_2}}{Pa_{CO_2}}$$

Statistical analysis was done by paired *t* test. Values represent mean ± SEM. $P < 0.05$ was considered significant.

## RESULTS

The results are summarized in table I. Mean arterial pressure was reduced by 40.8% during induced hypotension ($P < 0.01$) and returned to the control value during the recovery period. Mean pulmonary artery pressure and pulmonary capillary wedge pressure were essentially unchanged during the entire procedure. Cardiac index increased by 20% during induced hypotension ($P < 0.05$) and returned to control value during recovery. Neither the arterial carbon dioxide tension nor the pulmonary deadspace to tidal volume ratio changed in any of the three periods of measurement.

## DISCUSSION

We have demonstrated that during anaesthesia and nitroprusside-induced hypotension the pulmonary deadspace to tidal volume ratio is not increased. Thus the contention that deliberately induced hypotension always causes an increase in $V_D/V_T$ is refuted by this study.

$V_D/V_T$ in the anaesthetized, intubated and mechanically ventilated prone patient was found in the present study to be 31%. It has been shown in the awake human subjects that changing from the upright to the supine position reduced $V_D/V_T$ from 34% to 30% (Craig, Wahba and Don, 1971). We do not have data in the awake state, but our results are in agreement with published data obtained during anaesthesia (Nunn, 1977). Pulmonary disease may influence deadspace ventilation. Patients suffering from chronic lung disease, where there has been destruction of alveolar septa and capillaries, have an increased pulmonary deadspace because of emphysema and hypoperfusion (Donald et al., 1952). In such patients, a further increase in $V_D/V_T$ occurs with the induction of anaesthesia (Pietak et al., 1975). The patients in our study had no pulmonary disease, and we expect no change in $V_D/V_T$ with induction of anaesthesia.

In this study during deliberate hypotension induced with nitroprusside, mean arterial pressure was reduced from 76 ± 4 to 45 ±22 mm Hg. $V_D/V_T$ remained unchanged during hypotension. When hypotension is produced by haemorrhage, $V_D/V_T$ can increase to 55–64% (Cournand et al., 1943; Gerst, Rattenberg and Holaday, 1959). This occurs

TABLE I. *Haemodynamic and respiratory gas exchange values during nitroprusside-induced hypotension. Values represent mean ± SEM. Control* v. *hypotension, recovery* v. *hypotension:* *P < *0.01;* †P < *0.05*

| | Control | Hypotension | Recovery |
|---|---|---|---|
| Mean arterial pressure (mm Hg) | 76 ± 4 | 45 ± 2* | 77 ± 4 |
| Mean pulmonary artery pressure (mm Hg) | 13 ± 1 | 14 ± 1 | 14 ± 1 |
| Pulmonary capillary wedge pressure (mm Hg) | 7 ± 1 | 7 ± 1 | 8 ± 1 |
| Cardiac index (litre $m^{-2}$ $min^{-1}$) | 2.20 ± 0.1 | 2.60 ± 0.1† | 2.10 ± 0.1 |
| $Pa_{CO_2}$ (kPa) | 4.32 ± 0.27 | 4.29 ± 0.14 | 4.28 ± 0.27 |
| $V_D/V_T$ (%) | 33 ± 1 | 32 ± 1 | 34 ± 1 |

because haemorrhage results in hypovolaemia and subsequent pulmonary hypoperfusion, thereby increasing *V*D/*V*T. Eckenhoff and his co-workers (1963) in their landmark paper showed that during nitrous oxide in halothane anaesthesia, deliberate hypotension with trimethaphan or pentolinium and a head-up tilt caused *V*D/*V*T to increase to 75%. This observation was repeated by Askrog, Pender and Eckenhoff (1964). Anaesthesia, vasodilatation and pooling of blood in the periphery all combined to reduce venous return. Any decrease in filling pressure will result in diminished pulmonary blood flow and therefore will increase pulmonary deadspace (Nunn, 1977). Although in the above-mentioned studies pulmonary artery pressures were not measured, it is now well recognized that ganglionic blocking agents, like haemorrhage, bring about a reduction in filling pressures. Ganglionic blocking agents have been shown to decrease cardiac output probably by the same mechanisms (Scott et al., 1972). It has been shown that a decrease in cardiac output results in an increase in *V*D/*V*T (Suwa, Hedley-Whyte and Bendixen, 1966).

In contrast to deliberate hypotension with ganglionic blocking agents, in our study with nitroprusside we observed no change in pulmonary artery pressures or pulmonary capillary wedge pressures. This was accomplished by giving adequate volume to fill the increased vascular capacity. The patients received a total of 3 litres of crystalloid fluid, 2 litres before hypotension and 1 litre during hypotension as has been our practice (Khambatta et al., 1978). This not only kept up filling pressures during hypotension, but it also permitted cardiac output to increase via afterload reduction and preload augmentation. In another study during nitrous oxide–halothane anaesthesia, intermittent positive pressure ventilation and deliberate hypotension with nitroprusside, an increase in *V*D/*V*T from 49% to 54% was noted (Wildsmith, Drummond and MacRoe, 1975). However, neither pulmonary artery pressures nor cardiac output were measured and no attempt was made to hydrate the patients during nitroprusside-induced vasodilatation. It is thus quite possible that the observed increase in *V*D/*V*T was the result of a decrease in filling pressures and cardiac output. Moreover, these patients had high *V*D/*V*T values under anaesthesia, indicating possible pulmonary disease, which is often managed during anaesthesia with underhydration.

We conclude that deliberate hypotension, *per se*, does not cause an increase in *V*D/*V*T. Moreover, we believe that maintenance of adequate hydration, filling pressures and cardiac output during induced hypotension play a crucial role in maintaining the normal pulmonary deadspace.

## REFERENCES

Askrog, V. F., Pender, J. W., and Eckenhoff, J. E. (1964). Changes in physiological deadspace during deliberate hypotension. *Anesthesiology*, 25, 744.

Cournand, A., Riley, R. L., Bradley, S. E., Breed, E. S., Noble, R. P., Lawson, M. D., Gregersen, M. I., and Richards, D. W. (1943). Studies of circulation in clinical shock. *Surgery*, 13, 964.

Craig, D. B., Wahba, W. M., and Don, M. F. (1971). Airway closure and lung volumes in surgical positions. *Can. Anaesth. Soc. J.*, 18, 92.

Donald, K. W., Renzetti, A., Riley, R. L., and Cournand, A. (1952). Analysis of factors affecting the concentration of oxygen and carbon dioxide in gas and blood of lungs: Results. *J. Appl. Physiol.*, 4, 497.

Eckenhoff, J. E., Enderby, G. E. H., Larson, A., Eldridge, A., and Judevine, D. E. (1963). Pulmonary gas exchange during deliberate hypotension. *Br. J. Anaesth.*, 35, 750.

Gerst, P. H., Rattenberg, C., and Holaday, D. A. (1959). The effect of hemorrhage on pulmonary circulation and respiratory gas exchange. *J. Clin Invest.*, 38, 524.

Gray, T. C., Nunn, J. F., and Utting, J. E. (1980). *General Anaesthesia*, 4th edn, p. 1149. London: Butterworths.

Khambatta, H. J., Stone, J. G., Matteo, R. S., and Michelsen, W. J. (1978). Hypotensive anesthesia for spinal fusion with sodium nitroprusside. *Spine*, 3, 171.

Nunn, J. F. (1977). *Applied Respiratory Physiology*, 2nd edn, p. 229. London: Butterworths.

Pietak, S., Weenig, C. S., Hickey, R. F., and Fairley, H. B. (1975). Anesthetic effects on ventilation in patients with chronic obstructive pulmonary disease. *Anesthesiology*, 42, 160.

Scott, D. B., Stephen, G. W., Marshal, R. L., Jenkinson, J. L., and MacRoe, W. R. (1972). Circulatory effects of controlled arterial hypotension with trimethaphan during nitrous oxide halothane anaesthesia. *Br. J. Anaesth.*, 44, 523.

Suwa, K., Hedley-Whyte, J., and Bendixen, H. H. (1966). Circulation and physiologic deadspace changes on controlling the ventilation of dogs. *J. Appl. Physiol.*, 21, 1855.

Wildsmith, J. A. W., Drummond, G. B., and MacRoe, W. R. (1975). Blood-gas change during induced hypotension with sodium nitroprusside. *Br. J. Anaesth.*, 47, 1205.

## EFFET D'UNE HYPOTENSION PROVOQUEE PAR LE NITROPRUSSIATE DE SODIUM SUR L'ESPACE MORT PULMONAIRE

### RESUME

Une hypotension provoquée au nitroprussiate entraîne une baisse de 40% de la pression artérielle moyenne, sans modification du rapport espace mort pulmonaire sur volume courant (*V*D/*V*T). Ceci est obtenu par une hydratation correcte à la fois avant et pendant l'hypotension, comme le montrent les pressions de remplissage inchangées. Aussi nous avons montré qu'une hypotension délibérée n'augmente pas par elle-même *V*D/*V*T et

que la vasodilatation peut démasquer une hypovolémie relative et être responsable de l'augmentation de $V_D/V_T$ observée par de précédents chercheurs.

## AUSWIRKUNG DER DURCH NATRIUMNITROPRUSSID HERVORGERUFENEN HYPOTONIE AUF DEN LUNGENTOTRAUM

### ZUSAMMENFASSUNG

Kontrollierte Blutdrucksenkung führte zu 40%iger Herabsetzung des mittleren arteriellen Blutdruckes, veränderte aber nicht das Verhältnis von Totraum zu Atemzugvolumen ($V_D/V_T$). Dies wurde durch angemessene Flussigkeitszufuhr vor und während der Blutdrucksenkung erreicht, wie man aus den konstanten Füllungsdrücken ersehen konnte. Damit haben wir gezeigt, daß die kontrollierte Blutdrucksenkung an sich nicht su einer Vergrösserung des Verhältnisses $V_D/V_T$ führt. Die Vasodilatation kann aber einen relativ hypovolämischen Zustand herbeiführen und damit für den Anstieg von $V_D/V_T$ verantwortlich sein, der von früheren Untersuchern beobachtet wurde.

## EFECTO DE LA HIPOTENSIÓN INDUCIDA POR NITROPRUSIATO DE SODIO SOBRE EL PERIODO MUERTO PULMONAR

### SUMARIO

Una hipotensión intencional con nitroprusiato tuvo por efecto una reducción del 40% de la presión arterial media, pero no provocó ningún cambio en la relación del periodo muerto pulmonar con el volumen respiratorio ($V_D/V_T$). Se consiguió este resultado mediante hidratación adecuada tanto antes como durante la hipotensión, tal como indicado por las presiones de relleno constantes. Entonces, hemos demostrado que la hipotensión intencional en sí no hace aumentar el $V_D/V_T$ y que la vasodilatación puede causar un estado relativamente hipovolémico y dar origen al aumento del $V_D/V_T$ observado por investigadores anteriores.

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# REDUCTION OF HEAT LOSS IN NEUROSURGICAL PATIENTS USING METALLIZED PLASTIC SHEETING

J. L. A. TELFER BRUNTON, G. M. M. THOMS AND I. BLAIR

SUMMARY

Metallized plastic sheeting (m.p.s.) was used in 14 neurosurgical patients and changes in body heat content during surgery compared with those of 14 control patients. All patients, except three in the study group and one in the control group, lost heat by the end of the operation. There was, however, a statistically significant reduction in heat loss in the patients wrapped in m.p.s. Measurement of skin temperature offers an important contribution to management of heat balance during anaesthesia.

It is well recognized that heat losses frequently occur in patients during anaesthesia and surgery. This may be because of relatively low ambient temperature, administration of cold i.v. fluids, use of unhumidified gases, evaporation from body cavities, metabolic depression by drugs and loss of muscle activity. The resulting hypothermia can produce physiological disturbances during the recovery period (Vale and Lunn, 1969), when the heat loss is regained by a combination of shivering and vasoconstriction (Hall, 1978). Oxygen consumption has been shown to increase by up to 486% (Bay, Nunn and Prys-Roberts, 1968). There may also be marked cardiovascular instability, in particular acute arterial hypertension (Holdcroft, 1980).

Metallized plastic sheeting (m.p.s.) acts by reducing heat loss from radiation, but also reduces convectional losses by excluding draughts. The use of m.p.s. in neurosurgical patients has been studied by Radford and Thurlow (1979). They compared core (oesophageal) temperatures of insulated and uninsulated patients and concluded that, in this respect, m.p.s. had no advantage over the use of a cotton blanket alone. In our neurosurgical unit it has been normal practice to wrap patients in m.p.s., since we had developed the clinical impression that m.p.s. reduced the problems of hypothermia in the recovery period. We therefore repeated the study examining heat balance rather than core temperature alone.

### *Measurement of changes in body heat content*

The relative contributions to mean body temperature $\bar{T}$, from core and mean skin temperature were derived by Burton (1935) as:

$$\bar{T} = 0.66\ T_c + 0.34\ \bar{T}_{sk}$$

where $T_c$ = core temperature and $\bar{T}_{sk}$ = mean skin temperature (°C).

Changes in heat content, $\Delta H$, can then be calculated, in kilojoules, as shown:

$$\Delta H = \text{sp.ht.} \times M \times \Delta \bar{T}$$

where sp.ht. = specific heat of body tissues ($3.47\ \text{kJ kg}^{-1}\,°\text{C}^{-1}$), $M$ = body weight (kg), $\Delta \bar{T}$ = change in mean body temperature.

### *Mean skin temperature*

Mean skin temperature is the average temperature of the skin over the whole body and cannot be measured precisely. The techniques of measuring mean skin temperature ($\bar{T}_{sk}$) have been evaluated by Shanks (1975), who concluded that preferably at least 10 skin sites should be used for an unweighted mean or, when access was limited, a reasonable approximation can be obtained by the four-point technique of Ramanathan (1964):

$$\bar{T}_{sk} = 0.3\ (\text{nipple} + \text{arm}) + 0.2\ (\text{thigh} + \text{calf})$$

Because of surgical requirements our choice of sites was restricted. We used the four-points recommended by Ramanathan and an additional six sites

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were selected as shown in fig. 1, in order to obtain an unweighted mean of 10 sites.

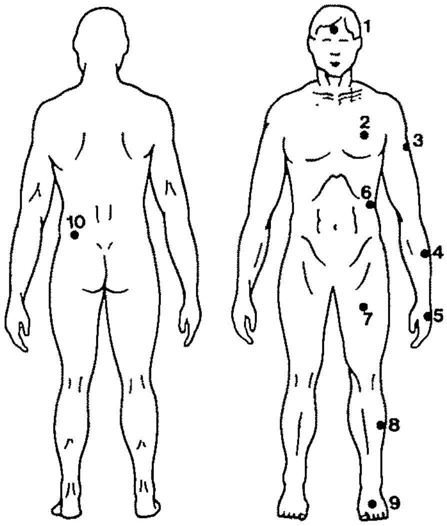

FIG. 1. Sites of temperature sampling.

## METHOD

Twenty-eight patients, aged 24–74 yr, undergoing elective craniotomy in the supine position were allocated to either the study group (insulated with m.p.s.) or the control group (no m.p.s.). Patients with pyrexia before operation, or alteration in level of consciousness, were excluded.

All patients wore a cotton theatre gown and anti-embolism stockings and were covered with one cotton blanket. On arrival in the anaesthetic room the 14 study patients were additionally covered with a heavyweight "Space Blanket" (Thermos) and before moving into theatre this was tucked under the patient so as to enclose all except the head and shoulders and the distal parts of the arm cannulated for i.v. infusion.

Premedication with oral lorazepam or diazepam was given 2 h before induction. Anaesthesia was induced with thiopentone and suxamethonium and, after tracheal intubation, controlled ventilation was established using nitrous oxide and oxygen. This was supplemented by an infusion of Althesin and fentanyl, or by increments of pethidine, and some patients received 0.5% halothane. Neuromuscular blockade was maintained using alcuronium or tubocuraine, and if required hypotension was induced using an infusion of sodium nitroprusside.

At induction, venous and arterial cannulae were introduced and the arterial pressure, e.c.g. and end-tidal carbon dioxide concentration subsequently monitored. The last value was maintained at 3–4%. I.v. fluids were given at room temperature and any blood transfusion required was administered through a blood warmer. All patients had intra-operative intermittent calf compression with inflatable leggings. After induction of anaesthesia an oesophageal thermistor probe was inserted until it was judged to lie at the nipple line and a rectal thermistor was introduced. The skin thermistors were taped in place, thermistors 3, 4 and 5 being on the arm opposite to the i.v. infusion.

Temperature measurements were made using a specially designed 12-channel electro-thermometer (Telemechanics). The thermistors were compared with mercury-in-glass thermometer over the range 25–40 °C and were shown to correspond to within ±0.1 °C. Theatre temperatures were measured to within ±0.1 °C at the beginning and end of surgery. Relative humidity was constant at 50%. Temperature recordings were made just before entering theatre and at 30-min intervals until the end of surgery. Changes in heat content were calculated, in kJ, for each 30-min interval. Statistical analysis of the data was confined to the first 3.5 h of surgery because of insufficient patient numbers beyond this interval.

## RESULTS

The comparability of the control and study group was examined, and the frequency of possible variables tabulated (table I). The two groups were similar with respect to sex, age, weight, duration of surgery, initial rectal temperature and theatre temperatures. The control group had a greater frequency of aneurysm surgery and use of sodium nitroprusside and a smaller frequency of halothane use.

Mean rectal temperatures for the two groups are shown in figure 2. There was no significant difference between the two groups (Student's *t* test), but a progressive and significant reduction within each group with time. Oesophageal temperatures were similarly examined and gave similar results, thus confirming the findings of Radford and Thurlow (1979).

The mean changes in heat content from the initial observation for the two groups of patients are shown in figure 3, using the four-point technique for deriving $\bar{T}_{sk}$. At 60 min and each 30-min interval subsequently, there was a highly significant difference between groups ($P < 0.01$). Using the 10-point sys-

TABLE I. *Comparison of study and control groups*

| | M.p.s. group | Control group |
|---|---|---|
| Proportion of males (%) | 64 | 64 |
| Age (yr) (mean ± SD) | 52.6 ±13.5 | 47.8 ±11.2 |
| Body weight (kg) (mean ± SD) | 69.2 ±13.4 | 62.3 ±11.5 |
| Duration of operation (h) (mean ± SD) | 4.18± 0.98 | 3.84± 1.02 |
| Proportion of aneurysm surgery (%) | 50 | 79 |
| Drugs used (%) | | |
| Halothane | 35.7 | 21.4 |
| Nitroprusside | 35.7 | 42.9 |
| Initial rectal temperature (°C) (mean ± SD) | 36.9 ± 0.6 | 36.8 ± 0.4 |
| Theatre temperature (°C) (mean ± SD) | | |
| Start | 22.7 ± 0.7 | 22.7 ± 0.8 |
| Finish | 22.7 ± 0.52 | 22.8 ± 1.2 |

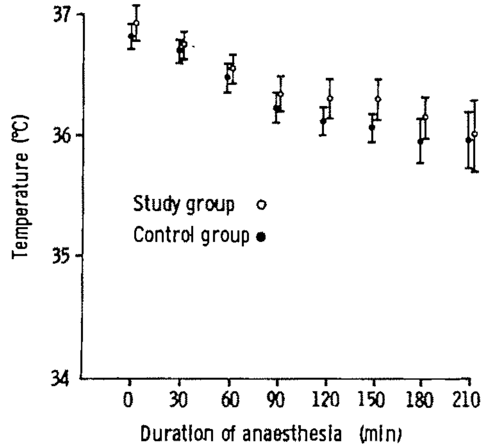

FIG. 2. Mean rectal temperatures for the two groups.

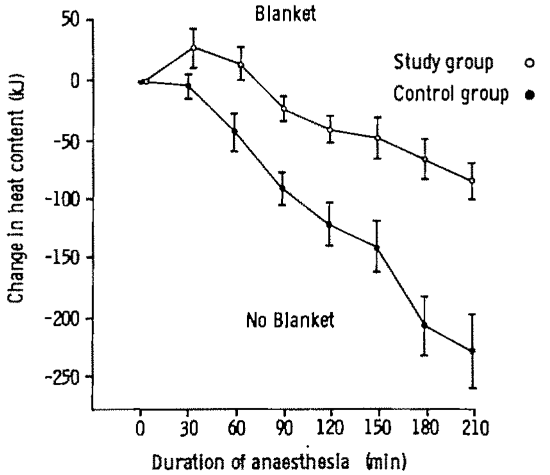

FIG. 3. Mean changes in heat content from the initial observation for the two groups, using the four-point technique for deriving $\bar{T}_{sk}$.

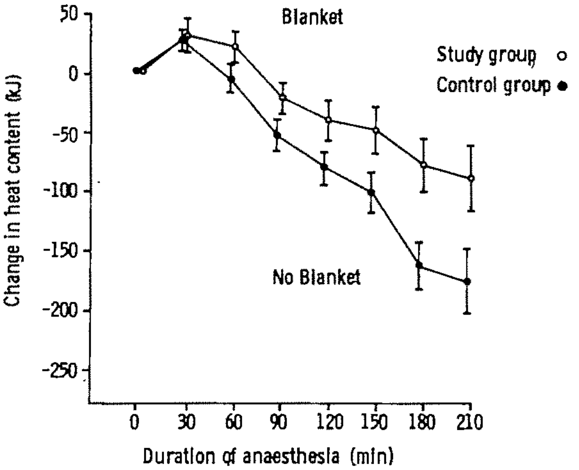

FIG. 4. Mean changes in heat content calculated using the 10-point system.

tem, mean changes in heat content were also calculated; the results are shown in figure 4. At 90 min and each subsequent 30-min interval there was a statistically significant difference between the groups ($P<0.05$).

## DISCUSSION

During the 3.5-h period studied, we have shown that there was no significant difference between the two groups in either rectal or oesophageal temperatures. This confirms the findings of Radford and Thurlow (1979). However by examining, in addition, changes in heat content we have shown that m.p.s. is of value in reducing heat loss during long neurosurgical operations.

In 1935 Burton calculated that 50% of the body mass lies within 2.5 cm of the skin surface, thus highlighting the importance of inclusion of skin temperature in estimating mean body temperature, and hence changes in body heat content. Of the patients in the study group, three of 14 had no loss of heat during anaesthesia, despite having significant decreases in rectal temperature. One of the 14 control patients had no significant decrease in heat content and was atypical in that he showed an increase in rectal temperature from start to finish during surgery.

We used rectal temperature measurements for core temperature in our calculations as suggested by Burton (1935). Although changes in rectal temperature lag behind oesophageal temperatures, we believe the time intervals between observations to be sufficient for this to be unimportant. Oesophageal probes are also more difficult to position accurately at the desired level in the lower quarter of the oesophagus (Whitby and Dunkin, 1968). At higher levels in the oesophagus large variations can occur because of the proximity of the trachea and the pulmonary veins.

It might be expected that choice of anaesthetic agent and theatre temperature could influence patient heat balance. Morris (1971) has shown that the choice of anaesthetic agent does not significantly influence the patient's body temperature. He has also examined the effect of ambient temperature and showed that theatre temperatures of 24–26 °C were required to prevent hypothermia in uninsulated patients. These values may be uncomfortably warm for the theatre personnel and, in our study, theatre temperatures were between 21 and 24 °C.

Holdcroft and Hall (1978) have also demonstrated that at a constant theatre temperature of 24 °C, body temperature changes were unrelated to either the type of anaesthesia or the percentage of subcutaneous fat to body weight.

Estimation of mean skin temperature during anaesthesia presents problems. While its measurement has been assessed in patients covered with surgical drapes (Shanks, 1975) no comparable studies have been carried out in patients wrapped in m.p.s. A critical evaluation of the methods for estimating mean skin temperature in insulated patients is outwith the scope or intent of this present study.

Since the head, shoulders and distal part of one arm were uninsulated, our study patients would be subject to different cooling influences in the theatre. However, we thought it probable that the effect of these differences would be small. We also used two different methods of estimating mean skin temperature. The four-point "weighted" method of Ramanathan involved four sites, all within the m.p.s. cocoon, while the "unweighted" mean of 10 skin sites included one point outside the m.p.s. covering. The four-point method has been shown to give results to within 0.2 °C of the 15-point formula of Winslow (Holdcroft and Hall, 1978). Our data show that both methods resulted in a significant reduction in heat loss in the m.p.s. group.

While we have shown that the use of m.p.s. does reduce heat loss during surgery, it did not prevent it in all cases. Active warming systems would be required in ensure normothermia. While the monitoring of core temperature is of value, particularly during prolonged operations, assessment of skin temperature provides further important information as to the total heat balance of the patient.

## ACKNOWLEDGEMENTS

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## REFERENCES

Bay, J., Nunn, J. F., and Prys-Roberts, C. (1968). Factors influencing arterial $P_{O_2}$ during recovery from anaesthesia. *Br. J. Anaesth.*, **40**, 398.

Burton, A. C. (1935). The average temperature in the tissues of the body. *J. Nutr.*, **9**, 264.

Hall, G. M. (1978). Body temperature and anaesthesia. *Br. J. Anaesth.*, **50**, 39.

Holdcroft, A. (1980). *Body Temperature Control.* London: Baillière–Tindall.

——Hall. G. (1978). Heat loss during anaesthesia. *Br. J. Anaesth.*, **50**, 157.

Morris, R. H. (1971). Operating room temperature and the anaesthetised paralysed patient. *Arch. Surg.*, **102**, 95.

Radford, P., and Thurlow, A. C. (1979). Metallized plastic sheeting in the prevention of hypothermia during neurosurgery. *Br. J. Anaesth.*, **51**, 237.

Ramanathan, N. L. (1964). A new weighting system for mean surface temperature of the human body. *J. Appl. Physiol.*, **19**, 531.

Shanks, C. A. (1975). Mean skin temperature during anaesthesia: as assessment of formulae in the supine surgical patient. *Br. J. Anaesth.*, **47**, 871.

Vale, R. J., and Lunn, H. F. (1969). Heat balance in anaesthetized surgical patients. *Proc. R. Soc. Med.*, **62**, 1017.

Whitby, J. D., and Dunkin, L. J. (1968). Temperature differences in the oesophagus. *Br. J. Anaesth.*, **40**, 991.

## DIMINUTION DE LA PERTE CALORIQUE EN NEUROCHIRURGIE GRACE A L'UTILISATION DE COUVERTURES PLASTIQUES METALLISEES

### RESUME

Nous avons utilisé des couvertures plastiques métallisées (CPM) chez 14 patients neurochirurgicaux et comparé les modifications du contenu calorique de l'organisme au cours de la chirurgie à celles de 14 sujets témoins. Tous les patients, sauf trois du groupe d'étude et un du groupe témoin, avaient perdu de la chaleur à la fin de l'intervention. Il y avait cependant une diminution statistiquement significative de cette perte chez les sujets enveloppés dans la CPM. La mesure de la température cutanée apporte une contribution importante au contrôle de la balance calorique au cours de l'anesthésie.

## DIE VERMINDERUNG DES WÄRMEVERLUSTES BEI NEUROCHIRURGISCHEN PATIENTEN DURCH VERWENDUNG VON PLASTIKTÜCHERN MIT METALLBESCHICHTUNG

### ZUSAMMENFASSUNG

Metallisierte Plastiktücher (m.p.s.) wurden bei 14 neurochirurgischen Patienten verwendet, und die Veränderungen der Körperwärme während der Operation mit 14 Kontrollpatienten verglichen. Alle Patienten ausser drei in der untersuchten Gruppe und einem in der Kontrollgruppe verloren gegen Ende der Operation Wärme. Bei den mit der m.p.s.-Folie geschützten Patienten gab es jedoch eine statistisch signifikante Verminderung des Wärmeverlustes. Die Messung der Hauttemperatur stellt einen wichtgen Beitrag zur Aufrechterhaltung des Wärmegleichgewichts während der Narkose dar.

## REDUCCIÓN DE LA PÉRDIDA DE CALOR EN PACIENTES DE NEUROCIRUJÍA POR USO DE HOJAS DE PLÁSTICO METALIZADO

### SUMARIO

Se usó hojas de plástico metalizado (m.p.s. *metallised plastic sheeting*) con 14 pacientes de neurocirujía y se llevó a cabo la comparación de la pérdida de calor corporal durante la cirujía de dichos pacientes con um grupo de control de 14 pacientes. Todos los pacientes, salvo tres en el grupo de estudio y uno en el grupo de control, perdieron calor al fin de la operación. Sin embargo, hubo una reducción significante desde el punto de vista estadístico en la pérdida de calor de los pacientes envueltos en las hojas de m.p.s. La medición de la temperatura de la piel contribuye grandemente al control del balance de calor durante la anestesia.

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# AIR AS A VAPORIZING GAS. COGNITIVE FUNCTIONS IN ELDERLY PATIENTS UNDERGOING ANAESTHESIA

F. N. PRIOR AND P. CHANDER

## SUMMARY

The effects of different anaesthetics on cognitive functions in elderly, air-breathing patients undergoing prostatectomy were studied and the results compared with those of patients who received oxygen additional to that in air. The patients received extradural anaesthesia, air and 3–4% ether, air and 0.5% trichloroethylene or nitrous oxide, oxygen and intermittent i.v. morphine or pethidine. The first three groups received no additional oxygen during or after operation; the fourth received oxygen for 12 h after operation. There were 15 patients in each group. The tests used were developed as appropriate for illiterate as well as educated patients. No deterioration of cognitive function was found in any group.

When it was found that major surgery under general anaesthesia which always included added oxygen in the inspired gas commonly resulted in a decrease in $Pa_{O_2}$ after operation (Nunn and Payne, 1962), many anaesthetists recommended the routine administration of oxygen during the early recovery period after operation. This practice is still favoured, although more on the grounds that an increased $Pa_{O_2}$ must be beneficial rather than on experimental proof that it is. Rigidly controlled experiments in man necessarily involve controls who receive no oxygen during or after operation. For ethical reasons, such investigations would be difficult.

In many parts of the world, a very large number of major operations are still performed with air as a vaporizing gas, no additional oxygen being used during or after surgery. The reason is simple enough: no oxygen is available or, at best, is very difficult to obtain and is therefore kept for the most urgent requirements. What harm is being done? We know that trichloroethylene is safe when given with air (Prior, 1972) and so is ether, although additional oxygen has been advised in the elderly as a precaution (Roberts et al., 1974). Measurement of $Pa_{O_2}$ may reveal mild hypoxaemia, but will give no information as to its effects on the patient. An assessment of cerebral function changes in terms of affect would be more realistic. Has there been a change in the patient's attitudes? Is he more irritable and difficult to get on with than before? That such things can happen was pointed out by Bedford (1955) many years ago, although it was later shown that many of the cases were emergencies (Simpson, 1961). Such changes, even if not catastrophic, can be very distressing for relatives and it seems reasonable to assume that they may be a result of a period of relative hypoxaemia during or after surgery. In this study, an attempt has been made to quantify one aspect of these changes with reference to memory, a part of cerebral function which is very sensitive to injury. Although oxygen is usually available in this hospital, a large proportion of anaesthetic trainees work in situations where it is not. Even here, there are times when it is difficult to obtain oxygen and therefore economy in its use must be practised. For these reasons we submit that this investigation is ethical, since no patient was subjected to anaesthetic procedures any different from common practice in this and many other Indian hospitals. It was decided to compare the effect on memory of a typical "Western" anaesthetic, based on nitrous oxide and oxygen including additional oxygen after operation, with that resulting from the techniques commonly applied here, which use air and no postoperative oxygen. Another approach would have been to use one technique with and without oxygen, but this obviously cannot be done if nitrous oxide is used and we did want to see how the use of air compared with the widely preferred techniques using oxygen during and after operation.

## METHODS

In order to standardize the surgery and operative risks as far as possible, patients over 55 years of age were chosen (range 55–83 yr, mean 65.6 yr). All

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were free of obvious cardiorespiratory diseases, and any patient suffering from such was excluded. Overt psychiatric and organic brain diseases were also excluded. Four groups of 15 patients each were studied.

Transvesical, suprapubic prostatectomy was chosen as a standard major operation which, here, lasts 1.5–2 h, with moderate blood loss, but is less liable than upper abdominal surgery to be followed by lung complications which may alter the findings irrespective of the anaesthetic given. At the same time the choice of elderly patients may be expected to show differences in cerebral function more readily than younger ones.

### *Anaesthetic procedures*

Successive admissions who qualified for the trial were given one of the following four anaesthetics with no other selection criteria. Anaesthetics were given in the same order to each of four successive patients as follows:

*Group I.* Extradural 2% lignocaine 18–20 ml. No additional oxygen during or after operation.

*Group II.* Air and 3–4% ether; controlling ventilation; gallamine. No additional oxygen.

*Group III.* Air and 0.5% trichloroethylene; controlling ventilation; gallamine. No additional oxygen.

*Group IV.* Oxygen in 60–70% nitrous oxide with small i.v. increments of morphine (up to 10 mg) or pethidine (up to 100 mg) and gallamine to allow control of ventilation. Nasal oxygen was continued for 12 h after operation at $F\text{I}_{O_2}$ approximately 0.35–0.40, using a catheter previously calibrated to transmit the actual flow shown on the flowmeter and using a nomogram previously worked out in this department relating $F\text{I}_{O_2}$ to flow (Thomas, 1978). In this nomogram, variations resulting from different minute volumes are allowed for.

In all patients receiving general anaesthesia thiopentone was given and the trachea intubated after relaxation with suxamethonium. The lungs were subsequently ventilated to a $P\text{CO}_2$ of about 4.6 kPa checked with the Campbell Howell rebreathing method.

### *Memory function tests*

Immediate, recent and remote memory were tested using the memory scale of the Postgraduate Institute, Chandigarh as standardized by Dwarka Pershad (Pershad, 1977).

Details of the memory scale and scoring system applied are given in the Appendix in English, although the tests were, of course, administered in the local vernacular.

The tests were developed in order to avoid the loading with intelligence requirements which is a feature of standard tests (Eysenck and Halstead, 1945; Wechsler, 1945; Wechsler and Stone, 1945; Pershad and Verma, 1975) so that they can be applied to illiterate as well as educated subjects. The reliability of the tests in terms of stability of the score was found to be good when retesting was performed after 1 week, the correlation coefficient varying in the range $r = 0.90-0.89$.

The correlation with the Boston Memory Scale was found to be 0.71 and with the Wechsler Memory Scale 0.85, although they cannot be used on an illiterate population. It has also been shown that the test score does diminish with age (Pershad and Dubey, 1974). For this reason the patients studied were chosen as all being in a fairly closely defined age range.

Item (9) was dropped from the scale because the study was only designed to measure memory changes for familiar things rather than the ability to learn. Also, the reproduction of new visual ideas which item (9) demands, is difficult for illiterate patients.

Testing was done 1 day before operation on all patients by the same observer and at 7 days after operation by a clinical psychologist who was unaware of the type of anaesthesia given. The data obtained were compiled and analysed only at the end of the study, comparing with standard scores for this age range. Both observers, however, administered preliminary tests to patients not included in the study, in order to check comparability between their results, and this was achieved. The results were subjected to a *t* test.

## RESULTS

The mean score of each group is shown in table I. The standard score (Pershad, 1977) is shown for comparison, but it should be noted that this is for a group of mean age 60.9 yr. The present study is concerned with a mean age of 65.6 yr.

There was no evidence of an overall deterioration in cognitive functions.

These results are shown graphically in figure 1. Every group improved its score after operation and there were no differences between the groups with respect to the amount of improvement. There were, in fact, six patients whose score deteriorated from 1

TABLE I. *Mean score for each group with ranges. Standard is for subjects of mean age 60.9 yr; present study mean is 65.6 yr*

| | Group I | Group II | Group III | Group IV | Standard |
|---|---|---|---|---|---|
| Before operation | 52 (38–63) | 49 (29–60) | 49 (26–60) | 49 (26–65) | 62.5 |
| After operation | 60 (46–70) | 56 (27–69) | 56 (41–68) | 56 (44–70) | |
| Difference | + 8 (15%) | + 7 (14%) | + 7 (14%) | + 7 (14%) | |
| *t* | 4.9 | 4.2 | 4.7 | 4.9 | |
| Significance | n.s. | n.s. | n.s. | n.s. | |

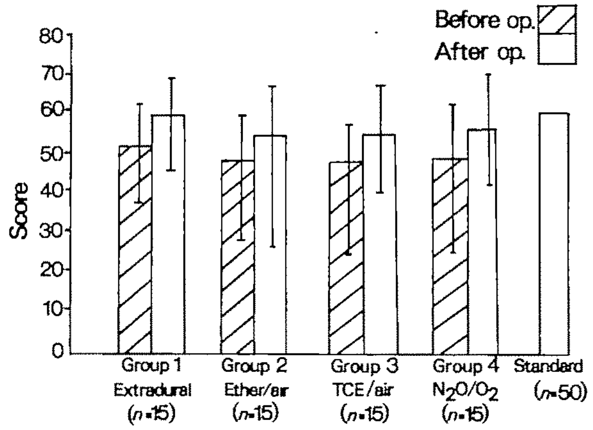

FIG. 1. Mean memory scores for each group with ranges, 1 day before and 7 days after prostatectomy.

to 6 points after operation. Two of these were in group I, one in group II, two in group III and one in group IV.

In case other factors influenced the results they were examined with regard to the patients' education. This ranged from illiteracy to college experience, but 40% had had no schooling and 52%, schooling up to matriculation. However, the level of literacy made no difference to the scores. Similarly, those who were from rural or urban background were compared and so were the varying professions represented in the study groups. Again, neither place nor type of work influenced the scores.

One patient died after operation, but subsequent to the postoperative testing.

## DISCUSSION

In a consideration of the effects of major surgery upon the older age group, it is not easy to isolate and evaluate possible causes of deterioration in mental function. These could be a result of the stress of operation, episodes of hypoxaemia, hypotension, drugs used, natural deterioration or a mixture of factors. It is clear enough that pure hypoxaemia is dangerous. Crow and Kelman (1971) showed that memory impairment was produced by simulating high altitudes. At the equivalent of 8000 ft ($P\text{I}_{O_2}$ 16 kPa) there was no change, but at 12000 ft ($P\text{I}_{O_2}$ 12.2 kPa) there was. Gilbertstadt and Sako (1967) demonstrated deterioration in intellectual functions after open heart surgery based on Wechsler's digit span and digit symbols. It was concluded that repeated heart failure and consequent transient hypoxic episodes were the causes of the deterioration.

Patients undergoing prostatectomy were studied by Rollason and others (1971) using spinal analgesia to produce hypotension, with and without a vasopressor. They used a battery of tests, including memory, and found no differences before and after operation. Hypotension was not a problem in the present series, steps being taken to prevent it in the extradural group by giving an i.v. infusion.

The drugs used could also contribute to hypoxia, but those that might have done so would tend to cause an adverse effect in all groups receiving them. All had morphine or pethidine before operation, both respiratory depressants. Three groups given general anaesthesia had thiopentone and relaxants in addition, but the former would have declined to a small blood concentration long before the conclusion of surgery, and very soon after its administration ventilation was controlled. Very low concentrations of ether or trichloroethylene were subsequently used in two groups and nitrous oxide in oxygen with intermittent i.v. morphine or pethidine in another. The extradural group could have included cases with respiratory depression as a result of a high block, although this was not observed. In all cases, however, if there was any effect because of drugs it would have been to decrease the cognitive functions score.

It is also a problem to decide which tests of mental function are going to be the most informative.

Drummond (1975), in an extended review of many types of tests, concluded that short-term memory and flicker fusion were the most sensitive, simple, reproducible and discriminating. For these reasons the present study relied on a memory scale which is easily applicable to all types of patients whether educated or illiterate. The scale was developed in the Postgraduate Institute in Chandigarh and was chosen because it has been standardized on a population within the socio-economic dimensions of Punjab. It is comparable in design and sensitivity to similar scales developed in Western countries, is simple to apply and does not need interpretation by an expert clinical psychologist. Bias was minimized by having different investigators use the test before and after operation, and by not knowing what anaesthetic had been given. Results were reasonably consistent within and across the four groups studied. Details of the scoring system are given in the appendix.

Eight of the components of the test are for auditory and two for visual stimuli, in keeping with the observation that auditory stimuli are more important than visual (Bower, 1975). The visual test, No. 9, posed difficulties in patients with early cataracts, so the tests were given without this visual component. The designer of the scale has pointed out that the omission of one component does not affect the overall sensitivity. In these cases an average of eight points for visual retention and reproduction was added to the total, in keeping with the standard scores.

The study was designed specifically to see if restriction of oxygen to that available in the air led to deterioration in memory function as compared with a group who received high oxygen concentrations during and after surgery. The fact has to be faced that a very large number of anaesthetics given in the world, probably the majority, have still to be given without extra oxygen simply because it is not available. Travelling round small hospitals in various parts of India over the past 20 years has impressed one author with both the amount of major surgery which is done and with the good results in terms of mortality. Morbidity figures, however, are almost impossible to obtain. Most of these hospitals find it so difficult to obtain oxygen that, if they do get supplies, these are, understandably, kept for those in obvious and urgent need. These conditions have to be kept in mind whilst teaching postgraduates in this hospital who are, in many cases, aiming to work where oxygen is scarce. Over the years we have not been able to demonstrate any adverse effects of air as an anaesthetic vehicle on mortality or morbidity, but the more sensitive testing of mental function had not been done.

The preoperative scores were equivalent to the standardized scores of neurotic subjects, but almost all increased to a normal figure at postoperative testing, regardless of the type of anaesthetic. It must be remembered that the standardized scores were for patients with a mean age 5 years less than the group now under review. Nevertheless, although it may at first seem odd to imply that surgery and anaesthesia improve mental function, this is not difficult to understand. Patients were admitted specifically for surgery and, already subjected to a battery of clinical tests, had to face this psychological test also. Nervousness and pre-occupation with the outcome of surgery would naturally lead to a tenseness which makes concentration on such tests difficult. The standardized tests were, of course, not conducted in a situation of stress. After operation, patients were more relaxed, thankful for a successful outcome of surgery and looking forward to going home quite soon.

The results suggest that in elderly, otherwise fit patients presenting for suprapubic prostatectomy, air is an adequate vehicle for anaesthetic vapours so that it is possible to exercise drastic economy in the use of oxygen, where it is scarce, without risk to the patient, provided that the basic principles of anaesthesia are observed. This however, does not indicate what the outcome might be after upper abdominal surgery in comparable groups of patients.

## APPENDIX

### MEMORY TEST OF POSTGRADUATE INSTITUTE, CHANDIGARH

(1) Remote memory (i.e. more than 48 h) Score 6

1. How old are you?
2. Where were you born?
3. When did you get married, start working and complete school studies?
4. What is the age of your youngest child, brother or sister?
5. When did you first come to this hospital for treatment?

Score for five correct answers is 6, diminishing by one for each incorrect answer.

(2) Recent memory Score 5

1. What did you have for dinner last night?
2. What did you have for breakfast this morning?
3. What is the name of this month?
4. What day is it today?
5. Who came to see you yesterday?

Score 1 for each correct answer.

(3) Mental balance Score 9
1. Repeat the alphabet
2. Say the numbers 0–20 in reverse order
3. Say the numbers 40–3 in reverse order
Maximum for each part is 3 if correct within 15 s; 2 if more than 15 s, 1 if one mistake and 0 if more than one.

(4) Attention and concentration Score 15
1. Repeat the following numbers after me... (e.g. 5, 7, 3)
2. Repeat the following numbers in reverse order... (e.g. 8, 5, 3)
Score maximum of 15 based on numbers of digits in the longest series correctly reproduced, backward and forward.

(5) Delayed recall Score 10
Names of a few familiar things are given at 1-s intervals; Patient asked to repeat them after 1 min.
Scoring 1 for each word correctly recalled, up to a maximum of 10.

(6) Immediate recall.
Three simple sentences are given and they are to be repeated in the same order.
The sentences, given with increasing difficulty, are scored 3, 4 and 5 respectively.

(7) Verbal retention for similar pairs Score 5
Scoring 1 for each correct reproduction of the associated word of the pair up to a maximum of 5.

(8) Verbal retention for dissimilar pairs Score 15
Scoring 5 for each of three trials as in (7)

(9) Visual retention Score 13
Having been shown some figures, asked to draw them after 30 s. This was omitted because of visual difficulties of the old patients studied. Total score adjusted to compensate.

(10) Recognition Score 10
A card with pictures of familiar things was shown, then another card which included the previously shown pictures along with others. Patient asked to recognize the original ones.
Each object correctly identified scored 1 and those identified but named or wrongly named, scored ½. Numbers of wrong identifications deducted from score.

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## REFERENCES

Bedford, P. D. (1955). Adverse cerebral effects of anaesthesia on old people. *Lancet*, 2, 259.

Bower, D. (1975). A multicomponent theory of memory trace; in *Human Memory, Basic Processes*, p. 437. N.Y., London and San Francisco: Academic Press.

Crow, T. J., and Kelman, G. R. (1971). Effect of mild acute hypoxia on human short term memory. *Br. J. Anaesth.*, **43**, 548.

Drummond, G. B. (1975). The assessment of post-operative mental functions. *Br. J. Anaesth.*, 47, 130.

Eysenck, H. G., and Halstead, H. (1945). The memory function. A factorial study of fifteen clinical tests. *Am. J. Psych.*, **102**, 174.

Gilbertstadt, H., and Sako, V. (1967). Intellectual and personality changes following open heart surgery. *Arch. Gen. Psychiatr.*, **16**, 210.

Nunn, F. J., and Payne, J. P. (1962). Hypoxaemia after general anaesthesia. *Lancet*, 2, 631.

Pershad, D. (1977). The construction and standardization of a clinical test of memory in simple Hindi. Agra: National Psychological Corporation.

—— Dubey, B. L. (1974). Some experience with a memory test in the aged cases. *Ind. J. Psychol.*, **49**, 305.

—— Verma, S. K. (1975). Evaluation of Boston memory scale. *Ind. J. Clin. Psychol.*, 2, 51.

Prior, F. N. (1972). Trichloroethylene in air with muscle relaxants. *Anaesthesia*, 27, 66.

Roberts, J. G., Prys-Roberts, C., Moore, M. A., and Frazer, A. N. I. (1974). Cardio-pulmonary function during ether/air/relaxant anaesthesia. A comparison with nitrous oxide/oxygen anaesthesia. *Anaesthesia*, 29, 4.

Rollason, W. N., Robertson, G. S., Cordiner, C. M., and Hall, D. L. (1971). A comparison of mental functions in relation to hypotensive anaesthesia in the elderly. *Br. J. Anaesth.*, **43**, 561.

Thomas, M. (1978). A study of intranasal oxygen. M.D. Thesis, Punjab University.

Simpson, B. R. (1961). The effects of anaesthesia and elective surgery on old people. *Lancet*, 2, 887.

Wechsler, D. (1945). A standardized memory scale for clinical use. *J. Psychol.*, **19**, 87.

—— Stone, C. P. (1945). Manual-Wechsler memory scale. New York: The Psychological Corp.

## L'AIR COMME GAZ VECTEUR. LES FONCTIONS SUPERIEURES DE SUJETS AGES SUBISSANT UNE ANESTHESIE

### RESUME

Nous avons étudié les effets de différents anesthésiques sur les fonctions supérieures de sujets âgés, respirant de l'air et devant subir une prostatectomie et comparé les résultats à ceux de sujets recevant de l'air enrichi en oxygène. Les patients bénéficiaient d'une anesthésie péridurale, d'air mêlé à de l'éther (3–4%), d'air contenant du trichloréthylène (0,5%) ou du protoxyde d'azote, d'oxygène et d'injections discontinues de morphine ou de péthidine. Les trois premiers groupes n'avaient pas d'apport supplémentaire d'oxygène pendant et après l'opération. Le quatrième groupe recevait de l'oxygène pendant 12 h après l'opération. Il y avait 15 patients dans chaque groupe. Les tests utilisés convenaient aussi bien à des illetttrés qu'a des personnes cultivées. Nous n'avons retrouvé dans aucun groupe de détérioration des fonctions supérieures.

## RAUMLUFT ALS ATEMGAS. DIE KOGNITIVEN FUNKTIONEN VON ÄLTEREN PATIENTEN WÄHREND DER NARKOSE

### ZUSAMMENFASSUNG

Die Auswirkungen verschiedener Narkosemittel auf die kognitiven Funktionen bei älteren Patienten, die während einer Prostatektomie Raumluft atmeten, wurden untersucht und mit den Ergebnissen von Patienten verglichen, die mit Sauerstoff angereicherte Luft zu atmen bekamen. Die Patienten erhielten eine Periduralanästhesie, Luft, und 3–4% Äther, Luft und Trichloräthylen 0,5%, oder Lachgas, Sauerstoff und intermittierend i.v. Morphium oder Pethidin. Die ersten drei Gruppen erhielten keinen zusätzlichen Sauerstoff während oder nach der Operation. Die vierte erhielt postoperativ 12 h Sauerstoff. In jeder Gruppe waren 15 Patienten. Die verwendeten Tests waren sowohl für gebildete als auch ungebildete Patienten geeignet. In keiner Gruppe wurde eine Störung der kognitiven Funktionen gefunden.

## EL AIRE COMO GAS DE VAPORIZACIÓN. FUNCIONES COGNOSCITIVAS EN PACIENTES DE EDAD BAJO ANESTESIA

### SUMARIO

Se llevó a cabo el estudio de los efectos de distintos anestéticos sobre las funciones cognoscitivas de pacientes de edad que respiraban aire y se encontraban sometidos a prostatectomía y los resultados fueron comparados con los de pacientes que recibían oxígeno adicional en el aire. Los pacientes recibieron una anestesia extradural, aire y éter al 3–4%, aire y tricloroetileno al 0,5% ó óxido nitroso, oxígeno y morfina o petidina i.v. intermitente. A los tres primeros grupos, no se les administró oxígeno adicional alguno durante o después de la operación: el cuarto grupo recibió oxígeno durante 12 h después de la operación. Había 15 pacientes en cada grupo. Las pruebas usadas correspondían tanto a pacientes analfabetos como a pacientes educados. No se encontró ningún deterioro de la función cognoscitiva en cualquiera de los grupos.

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# MORBIDITY IN MINOR GYNAECOLOGICAL SURGERY: A COMPARISON OF HALOTHANE, ENFLURANE AND ISOFLURANE

J. A. TRACEY, A. J. C. HOLLAND AND L. UNGER

## SUMMARY

A comparison was made between halothane, enflurane and isoflurane with regard to their suitability for minor gynaecological procedures in patients who would be leaving the hospital within 24 h of the anaesthetic. Seventy-five healthy patients were randomly allotted to one of three groups which received one of these anaesthetics. In respect of patient acceptance and postoperative morbidity there were no significant differences between halothane and enflurane, but after isoflurane there was a significantly greater frequency of minor sequelae (headache, nausea, dizziness and coughing) and its pungent odour made it unacceptable to some patients.

The past 2 years have seen the introduction of isoflurane to clinical practice in North American hospitals. The present study was designed to investigate postoperative morbidity in minor gynaecological surgery and to compare the influence of halothane, enflurane and isoflurane. Minor gynaecological procedures were chosen for comparison because the patient usually does not stay in the hospital for more than 24 h and therefore minor sequelae are a specially important consideration.

## PATIENTS AND METHODS

Seventy-five patients undergoing either dilatation and curettage (D&C) or laparoscopy were studied. They were assessed the night before by the anaesthetist and any patient with a medical disorder or who was taking medication was excluded from study. The remainder were then randomly allocated to one of three groups.

### *Anaesthetic technique*

No premedication was given. The anaesthetics were all given by one of the authors (J. T. or A. J. H.). In all patients anaesthesia was induced with thiopentone. If tracheal intubation was required, tubocurarine 3 mg was given to precurarize and suxamethonium 1 mg $kg^{-1}$ for muscle relaxation. If continuous muscle relaxation was required a suxamethonium drip (1 mg $ml^{-1}$) was used. A twitch monitor was used in all such cases. Anaesthesia was maintained with nitrous oxide in oxygen in a ratio of 2 : 1 and the inhalation agent allotted to the patient. The duration of each procedure was noted.

### *Assessment after operation*

Each patient was assessed on two occasions. The first assessment was made 1 h after being returned to the recovery room, immediately before discharge to the wards. The nursing staff noted the occurrence of nausea or vomiting and also any analgesics given.

The second assessment was made on the following morning just before discharge home and the patient completed a questionnaire at that time, in which she was asked about any symptoms she may have developed after operation. The interviewer on this occasion was not the anaesthetist and did not know to which group the patient belonged.

## RESULTS

Questionnaires were completed by a total of 75 patients. The Chi-squared test with Yates' correction was used to evaluate the significance of difference between the groups.

The three groups were similar in respect of age, weight and duration of operation as well as in numbers having D&C alone or laparoscopy (table I).

The most frequent symptoms after operation were sore throat (65%) and abdominal pain (61%), followed by shoulder tip pain (52%), feeling low in energy (38%), dizziness (33%), drowsiness (30%) and headache (25%) (table II).

There was no statistically significant difference

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TABLE I. *Comparison of age, weight, duration of operation (mean ± SD) and numbers in each group*

| Group | Age (yr) | Weight (kg) | Duration of operation (min) | D&C alone | Laparoscopy + D&C |
|---|---|---|---|---|---|
| Halothane | 34.5 ± 6.9 | 62.7 ± 10.9 | 40.2 ± 9.7 | 4(16%) | 21(84%) |
| Enflurane | 33.3 ± 6.0 | 61.9 ± 12.7 | 36.3 ± 11.2 | 5(20%) | 20(80%) |
| Isoflurane | 34.3 ± 11.2 | 56.3 ± 8.0 | 35.6 ± 11.2 | 5(20%) | 20(80%) |

TABLE II. *Postoperative morbidity in three groups of twenty-five patients. Number affected (% of group)*

| | Halothane | Enflurane | Isoflurane |
|---|---|---|---|
| First hour after operation | | | |
| Nausea | 4(16) | 9(36) | 4(16) |
| Vomiting | 3(12) | 5(20) | 3(12) |
| Number requiring analgesics | 0(0) | 3(12) | 5(20) |
| First day after operation | | | |
| Headache | 5(20) | 3(12) | 11(44) |
| Nausea | 2(8) | 3(12) | 8(32) |
| Vomiting | 1(4) | 1(4) | 3(12) |
| Dizziness | 4(16) | 7(28) | 13(52) |
| Drowsiness | 4(16) | 9(36) | 10(40) |
| Sore throat | 17(68) | 16(64) | 16(64) |
| Muscle aches | 4(16) | 7(28) | 5(20) |
| Back ache | 4(16) | 3(12) | 3(12) |
| Abdominal pain | 13(52) | 17(68) | 16(54) |
| Shoulder tip pain | 11(44) | 15(60) | 13(52) |
| Smell anaesthetic | 7(28) | 3(12) | 10(40) |
| Increased cough | 4(16) | 10(40) | 11(44) |
| Mind going blank | 0(0) | 0(0) | 1(4) |
| Low in energy | 7(28) | 11(44) | 11(44) |

between the responses of the enflurane group and the halothane group.

In the recovery room there were no significant differences found between the three groups in the frequency of nausea and vomiting. The isoflurane patients required significantly more analgesics than the halothane patients ($P < 0.02$).

On the first day after operation the isoflurane group had a significantly greater frequency of dizziness ($P < 0.01$), nausea ($P < 0.01$) and coughing ($P < 0.05$) than did the halothane group. They also had a greater frequency of headache ($P < 0.05$) and a greater number of them remembered the smell of the anaesthetic when compared with the enflurane group ($P < 0.05$).

## DISCUSSION

The number of patients complaining of sore throat and abdominal pain was found to be greater than in other recent studies (Hunt, Plantevin and Gilbert, 1979; Towey et al., 1979). However, 80% of patients in our study were undergoing laparoscopy and the trachea was intubated. If we analyse the figures for this group the frequency of sore throat is 73% and of abdominal pain 67%. Lignocaine jelly, which was used to lubricate the tubes, has recently been implicated as a cause of sore throat after operation (Loeser, Stanley and Jordan, 1980).

Although shoulder tip pain is recognized as being associated with laparoscopy we were surprised at the large percentage of patients who had this complaint (57% of the laparoscopy group).

Our findings are similar to those of Stanford, Plantevin and Gilbert (1979) in that we found no significant difference when comparing the halothane and enflurane groups.

The most interesting finding was the statistically significant greater frequency of a number of sequelae in the isoflurane group. The increased analgesic requirement of this group is probably a result of the more rapid excretion of anaesthetic and a subsequent shorter recovery period.

Increased cerebral blood flow has been postulated as the cause of headache after halothane anaesthesia (Tyrrell and Feldman, 1968). Isoflurane also causes cerebral vasodilatation (Cucchiara, Theije and Michenfelder, 1974; Adams et al., 1981) and this might explain the greater frequency of headache found in this group of patients.

The pungent smell of isoflurane makes it unsuitable for use as an induction agent. Despite an i.v. induction, 10 of the patients who received isoflurane remembered the smell and most described it as unpleasant. Only one patient complained of "your mind going blank" although an earlier study (Davison et al., 1975) had associated this symptom with isoflurane.

The present study confirms that there is a high morbidity rate after minor gynaecological surgery. It concludes that there is a greater frequency of minor sequelae (in particular headache, nausea, dizziness and cough) when isoflurane is used, thus making this a less suitable drug for this type of surgery than halothane or enflurane.

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## REFERENCES

Adams, R. W., Cucchiara, R. F., Gronet, G. A., Messich, J. M., and Michenfelder, J. D. (1981). Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. *Anesthesiology*, 54, 97.

Cucchiara, R. F., Theije, R. A., and Michenfelder, J. D. (1974). The effects of isoflurane in canine cerebral metabolism and blood flow. *Anesthesiology*, 40, 571.

Davison, L. A., Steinhelber, J. C. Eger, E. I., and Stevens, W. C. (1975). Psychological effects of halothane and isoflurane anesthesia. *Anesthesiology*, 43, 313.

Hunt, T. M., Plantevin, O. M., and Gilbert, J. R. (1979). Morbidity in gynaecological day-case surgery: a comparison of two anaesthetic techniques. *Br. J. Anaesth.*, 51, 785.

Loeser, E. A., Stanley, T. H., and Jordan, W. (1980). Postoperative sore throat: influence of tracheal tubes lubrication versus cuff design. *Can. Anaesth. Soc J.*, 27, 156.

Stanford, B. J., Plantevin, O. M., and Gilbert, J. R. (1979). Morbidity after day-case surgery: comparison of enflurane with halothane. *Br. J. Anaesth.*, 51, 1143.

Towey, R. M., Stanford, B. J., Ballard, R. M., and Gilbert, J. R. (1979). Morbidity of day-case gynaecological surgery: A comparison of thiopentone and Althesin. *Br. J. Anaesth.*, 51, 453.

Tyrrell, M. F., and Feldman, S. A. (1968). Headache following halothane anaesthesia. *Br. J. Anaesth.*, 40, 99.

## MORBIDITE EN CHIRURGIE GYNECOLOGIQUE MINEURE: COMPARAISON DE L'HALOTHANE, DE L'ENFLURANE ET DE L'ISOFLURANE

### RESUME

Nous avons comparé l'halothane, l'enflurane et l'isoflurane sous l'angle de leur intérêt pour des actes de gynécologie mineurs chez des patientes devant quitter l'hôpital moins de 24 h après l'anesthésie. Soixante-quinze patientes ont été réparties de façon aléatoire dans trois groupes, chaque groupe correspondant à un anesthésique. En ce qui concerne la tolérance par les patientes et la morbidité post-opératoire, il n'y avait pas de différences significatives entre l'halothane et l'enflurane, mais après l'isoflurane, il y avait une fréquence significativement plus grande de séquelles mineures (céphalées, nausées, sensation ébrieuse, et toux) et son odeur âcre l'a rendu insupportable à certaines patientes.

## MORBIDITÄT NACH KLEINEREN GYNÄKOLOGISCHEN EINGRIFFEN

### ZUSAMMENFASSUNG

Halothan, Enflurane und Isoenflurane wurden in Bezug auf ihre Eignung für kleinere gynäkologische Eingriffe bei Patienten verglichen, die innerbalb 24 h nach der Narkose das Krankenhaus wieder verlassen sollten. Fünfundsiebzig gesunde Patienten wurden nach Randomisierung einer von drei Gruppen zugeordnet, die je eines dieser Narkosemittel erhielten. In Bezug auf die Empfänglichkeit des Patienten und die postoperative Morbidität war kein Unterschied zwischen Halothan und Enflurane, aber nach Isoflurane traten kleinere Beschwerden (Kopfschmerzen, übelkeit, Schwindel und Husten) signifikant häufiger auf. Auch wurde es wegen seines unangenehmen Geruches von einigen Patienten nicht akzeptiert.

## MORBOSIDAD EN CIRUJÍA GINECOLÓGICA MENOR: UNA COMPARACION DEL HALOTANO, ENFLURANO E ISOFLURANO

### SUMARIO

Se llevó a cabo una comparación entre el halotano, el enflurano y el isoflurano respecto de su conveniencia para operaciones ginecológicas menores sobre pacientes que habían de dejar el hospital dentro de 24 h de la anestesia. Se distribuyó al azar setenticinco pacientes en cada uno de tres grupos a los que se administró uno de estos tres anestéticos. En lo que se refiere a la aceptación del paciente y a la morbosidad post-operatoria, no se observaron diferencias significantes entre el halotano y el enflurano, pero sí después del isoflurano, hubo una mayor frecuencia significativa de las secuelas menores (dolor de cabeza, nausea, vértigos y tos) y su olor acre no era aceptable para ciertos pacientes.

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# MYONEURAL ACTIONS OF ORG NC 45

T. A. TORDA AND N. KILOH

SUMMARY

In the toad sartorius preparation Org NC 45 reduced the mean quantal content of the end-plate potential both in magnesium- and tubocurarine-treated preparations, as well as blocking post-junctional receptors. In a concentration which permits recording of the miniature end-plate current no channel block was demonstrated.

Because of its short duration of action (Crul and Booij, 1980; Marshall, Agoston et al., 1980), lack of accumulation (Agoston et al., 1980; Buzello et al., 1980) and minimal side-effects (Marshall, Agoston et al., 1980; Marshall, McGrath et al., 1980; Agoston et al., 1980), Org NC 45 is likely to become widely used in clinical anaesthesia. Its effects on the chick biventer cervicis—reduction of the indirectly elicited twitch without contracture; reduction of response to acetylcholine—suggest a competitive, "non-depolarizing" and post-junctional mode of action (Durant et al., 1979). We report a series of electrophysiological studies to define more precisely the sites of action of the drug at the myoneural junction. Initial screening experiments (Torda and Kiloh, 1982) demonstrated that, at concentrations greater than that necessary to abolish indirectly evoked contraction, Org NC 45 reduces the mean quantal content ($m$) of the end-plate potential (EPP). Further studies were undertaken to demonstrate a presynaptic action at lesser concentrations, also to confirm the postsynaptic component of the neuromuscular block and to test for possible channel blocking action by examining the time course of the miniature end-plate current (MEPC).

## METHODS

The effect of Org NC 45 on quantal content of the end-plate potential (EPP) was investigated in two series of experiments on the toad (*Bufo marinus*) sartorius nerve–muscle preparation. The methods used are well known and have been described elsewhere in some detail (Torda, 1980). In the initial series muscle contraction was prevented by decreasing evoked acetylcholine release by the use of high magnesium solution containing: sodium chloride 115 mmol litre$^{-1}$, magnesium chloride 15–18 mmol litre$^{-1}$, potassium chloride 2.5 mmol litre$^{-1}$, calcium chloride 1.8 mmol litre$^{-1}$ and phosphate buffer (pH 7.2), 3 mmol litre$^{-1}$. The muscle was pinned out in a tissue bath and stimulated indirectly by supramaximal square wave pulses of 50 $\mu$s duration at 1 Hz frequency. The EPP were recorded through microelectrodes of 10–20 M$\Omega$ impedance and displayed on an oscilloscope. The mean amplitude and variance of 80 to 120 EPP was determined using a computer (PDP 8, Digital Equipment) and $m$ was calculated from the variance to mean ratio (Del Castillo and Katz, 1954). In two studies, 40 or more miniature end-plate potentials (MEPP) were also recorded and $m$ was also determined from the ratio of EPP to MEPP amplitude. As EPP in magnesium-treated preparations are small, correction for non-linear summation was not applied. After three to six determinations of $m$, the perfusing solution was changed to one containing Org NC 45 0.25 mg litre$^{-1}$ ($3.4 \times 10^{-7}$ mol litre$^{-1}$); after 20–30 min three to six further determinations were made. In three of the five cells, the preparation was then returned to control solution for further determinations of $m$. Early experiments, not reported here, using ampoule-packaged drug gave very variable results with inexplicable variations in quantal size. When fresh drug, dissolved in saline adjusted to pH 4.0 with hydrochloric acid was used, the results became reproducible. It is likely that the ampoule preparation underwent some interaction *in vitro*, which does not occur *in vivo*. Chelation with $Mg^{2+}$ ion is a possibility (D. Savage, personal com-

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munication). The pH of the Ringer's solution was not measurably affected by the small volume of acid drug solution added.

In the second series of experiments movement of the preparation was prevented by the addition of tubocurarine 1.2 mg litre$^{-1}$ ($1.5 \times 10^{-6}$ mol litre$^{-1}$), instead of magnesium ion. Similar determinations of $m$ were made in five cells with and without Org NC 45, 0.25 mg litre$^{-1}$; three cells were held long enough to complete wash-out of the drug to return to control conditions for further determinations.

Post-junctional block was demonstrated by recording the effect of Org NC 45 (0.25 mg litre$^{-1}$) on the amplitude of the miniature end-plate potential in four cells.

The effect of Org NC 45 in concentrations up to 0.5 mg litre$^{-1}$ on the rise-time and time constant of decay ($\tau_D$) of the MEPC was investigated using focal extracellular recording of the MEPC (Torda and Gage, 1977) in the presence of neostigmine, 1 mg litre$^{-1}$ ($3.0 \times 10^{-6}$ mol litre$^{-1}$). At each drug concentration MEPC were recorded on FM tape, which was later played back through a Neurograph N3 (Transidyne Corp.) transient recorder. For each estimate of $\tau_D$, 20 to 40 MEPC were "captured" and averaged by computer.

## RESULTS

The results from the five magnesium treated preparations are summarized in table I. Org NC 45 0.25 mg litre$^{-1}$ reduced mean quantal content of the EPP by an average of 50% (range 34–67%). The effect was readily reversible on wash-out.

TABLE I. *The effect of Org NC 45 0.25 mg litre$^{-1}$ on quantal content of the EPP of magnesium-treated preparations. The values obtained from EPP/MEPP ratio are not included in the means. The percent column expresses the treated value as percent of the mean of the control and washout values.* * *Value derived from EPP/MEPP ratio*

| | Quantal content | | | |
|---|---|---|---|---|
| Cell | Control | Org NC 45 | Washout | Percent |
| 1 | 9.91 | 5.03 | 9.16 | 53 |
| 2 | 3.79 | 1.24 | 4.11 | 31 |
| 3 | 1.97 | 0.65 | | 33 |
| 4 | 3.09 | 2.20 | 4.00 | 62 |
| | 2.68* | 1.35* | 4.20* | 39* |
| 5 | 3.80 | 2.06 | | 54 |
| | 4.54* | 2.89* | | 64* |
| Mean ±SD | 4.51±3.10 | 2.24±1.68 | 5.76±2.95 | 46.6±13.8 |

When tubocurarine was used to prevent movement of the fibres, the quantal content of the EPP was greater than in the magnesium-treated preparation (table II). The effect of Org NC 45 was very similar, however—average of 48% reduction (range 39 to 72%)—which was reversible. The membrane potential was not altered by the drug in either the magnesium- or the tubocurarine-treated preparations.

The amplitude of MEPP was reduced by an average of 55% (range 43–61%) by Org NC 45 0.25 mg litre$^{-1}$ in the four preparations studied (table III).

Finally, there was no significant effect on either the 20% to 80% rise-time or the time constant of decay of the MEPC by Org NC 45 in the concentrations tested, although the MEPC amplitude was reduced by up to 58% (table IV).

TABLE II. *The effect of Org NC 45 0.25 mg litre$^{-1}$ on quantal content of the EPP in curarized preparations. The percent column expresses the treated value as percentage of the mean of the control and washout values*

| | Quantal content | | | |
|---|---|---|---|---|
| Cell | Control | Org NC 45 | Washout | Percent |
| 1 | 28.9 | 8.2 | | 28 |
| 2 | 21.6 | 11.2 | 27.6 | 46 |
| 3 | 38.2 | 23.2 | | 61 |
| 4 | 41.5 | 20.4 | 44.4 | 47 |
| 5 | 14.8 | 10.0 | 18.2 | 61 |
| Mean ±SD | 29.0±11.2 | 14.6±6.7 | 30.1±13.3 | 48.5±13.3 |

TABLE III. *The effect of Org NC 45 0.25 mg litre$^{-1}$ on MEPP amplitude (mV). The percentages are based on the mean of the control and washout values*

| | MEPP amplitude | | | |
|---|---|---|---|---|
| Cell | Control | Org NC 45 | Washout | Percent |
| 1 | 1.14 | 0.45 | 1.15 | 40 |
| 2 | 1.17 | 0.55 | 1.26 | 45 |
| 3 | 1.32 | 0.57 | 1.60 | 39 |
| 4 | 1.34 | 0.68 | 1.05 | 57 |
| Mean ±SD | 1.24±0.10 | 0.56±0.09 | 1.27±0.23 | 45.3±8.3 |

TABLE IV. *The effect of Org NC 45 on the amplitude, growth time (20% to 80%) and time constant of decay ($\tau_D$) of MEPC in the neostigmine-treated toad sartorius*

| Concn ($\mu$g litre$^{-1}$) | Amplitude $\mu$V | Amplitude % | Growth (ms) | $\tau_D$ (ms) |
|---|---|---|---|---|
| Control | 208±42 | 100 | 0.56 | 3.55 |
| 5 | 193±30 | 93 | 0.54 | 3.30 |
| 10 | 194±50 | 93 | 0.54 | 3.92 |
| 20 | 146±42 | 70 | 0.55 | 3.32 |
| 50 | 145±45 | 70 | 0.55 | 3.92 |
| 100 | 138±36 | 66 | 0.53 | 3.70 |
| 500 | 87±16 | 42 | 0.54 | 3.20 |

## DISCUSSION

All the initial clinical studies to which reference has been made in the introductory paragraph confirm the clinical value of Org NC 45 as a relatively short-acting neuromuscular blocking drug with few side-effects. Its actions, as distinct from its effects, have been the subject of only one study to date (Durant et al., 1979). Screening experiments suggested that Org NC 45 in concentrations greater than that required to immobilize the indirectly-stimulated preparation, reduced the quantal content of the EPP (Torda and Kiloh, 1982).

Neuromuscular transmission can be interrupted in numerous ways. Interference with neurosecretion (reduction of quantal content of the EPP) is typical of the magnesium ion (Del Castillo and Katz, 1954) or the aminoglycoside antibiotics (Elmquist and Josefsson, 1962). The post-junctional receptors can be blocked competitively, as by tubocurarine (Jenkinson, 1960), or irreversibly as with α bungarotoxin (Katz and Miledi, 1973a). Decamethonium- and suxamethonium-induced block, usually called depolarization block, is also post-junctional in nature, although the exact mechanism must be considered uncertain or variable (Galindo, 1971a; Galindo and Kennedy, 1974; Adams and Sakman, 1978; Bowman, 1980). Additionally, at least three other possible mechanisms of transmission block exist. Desensitization by prolonged exposure to agonists (Rang and Ritter, 1970a; Bowman, 1980) and metaphilic antagonism, which is an interaction between a desensitizing drug and antagonist (Rang and Ritter, 1970b; Ryall, 1979). The final possible mechanism involves block of the open ionic channel. This is the type of action which local anaesthetics exert at the neuromuscular junction (Adams, 1976). Decamethonium in clinical concentrations appears to act as a channel blocker as well as whatever other actions it may have (Adams and Sakman, 1978) and tubocurarine has also been noted to affect the time constant of decay of MEPC in neostigmine-treated muscle (Katz and Miledi, 1973b) and under conditions of hyperpolarization, suggesting open channel block (Katz and Miledi, 1978; Colquhoun, Dryer and Sheridan, 1979). Gallamine and pancuronium may also have such action when the end-plate is hyperpolarized (Katz and Miledi, 1978). It was with these considerations in mind that the present series of experiments was planned. The mean open channel life-time was measured from the time constant of decay of the MEPC, which does not allow for investigation of the hyperpolarized state (Anderson and Stevens, 1973).

The effect of Org NC 45 on the MEPP confirmed a potent post-synaptic action, reversible and similar to the principal action of all the clinically used "non-depolarizing" neuromuscular blocking drugs. In a concentration of 0.25 mg litre$^{-1}$, Org NC 45 reduced the MEPP by 55%.

The experiments estimating quantal content confirmed that the MEPP is already reduced by concentrations of Org NC 45 less than that necessary to prevent muscle contraction. This is similar to the action of tubocurarine found by most workers (Galindo, 1971b; Hubbard and Wilson, 1973). A similar effect for pancuronium has also been described (Galindo, 1972a). It is likely that such prejunctional effect is of some significance, but its contribution to the clinical effect of these drugs is still open to speculation. Some believe that it is of considerable importance at physiological rates of nerve firing (Galindo, 1972b).

The theoretical significance of these findings is interesting. The work of Standaert (1964) and Standaert and Riker (1967) demonstrated that cholinergic drugs can act prejunctionally and that this action is blocked by tubocurarine. This work led to postulation of the existence of pre-junctional cholinergic receptors (Blaber and Karczmar, 1967; Hubbard, Wilson and Miyamoto, 1969) which may play a part in modulation of acetylcholine release (Bowman and Webb, 1976; Miyamoto, 1978). Block of these "$R_2$" receptors may result in reduced acetylcholine mobilization during tetanus and account for, or be a factor in, tetanic fade.

Finally, it has been suggested that open channel block as demonstrated by Katz and Miledi may also contribute to tetanic fade (Bowman, 1980). Our rather crude experiments failed to demonstrate such an effect for Org NC 45. In this context it is worth noting that shortening of open channel life-time by tubocurarine, pancuronium and gallamine has only been demonstrated in the hyperpolarized preparation and was undetectable at physiological membrane potential.

In summary, therefore, Org NC 45 reduces quantal content of the EPP, as well as blocking receptors competitively in the toad sartorius. Open channel block at normal membrane potential has not been demonstrated. Although these findings will not influence clinical practice, they have implications for a better understanding of neuromuscular transmission and of the drugs which block it.

## ACKNOWLEDGEMENTS

We are deeply indebted to Professor P. W. Gage of the School of Physiology and Pharmacology of the University of New South Wales for his help, encouragement and the use of his laboratory, to Ms J. Allen for much assistance and to Dr D. S. Savage of Organon Technica for supplies of NC 45 and Organon (Australia) for generous financial assistance; finally to our ever patient Ms Schubert for innumerable typescripts.

## REFERENCES

Adams, P. R. (1976). Drug blockage of open end-plate channels. *J. Physiol. (Lond.)*, **260**, 531.

—— Sakman, B. (1978). Decamethonium both opens and blocks end-plate channels. *Proc. Natl Acad. Sci. U.S.A.*, **75**, 2994.

Agoston, S., Salt, P., Newton, D., Bencini, A., Boosma, P., and Erdman, W. (1980). The neuromuscular blocking action of Org NC 45, a new pancuronium derivative, in anaesthetized patients. A pilot study. *Br. J. Anaesth.*, **52**, 53S.

Anderson, C. R., and Stevens, C. F. (1973). Voltage clamp analysis of acetylcholine produced end-plate current fluctuations at frog neuromuscular junction. *J. Physiol. (Lond.)*, **235**, 655.

Blaber, L. C., and Karczmar, A. G. (1967). Multiple cholinoceptors and related sites at the neuromuscular junction. *Ann. N.Y. Acad. Sci.*, **144**, 571.

Bowman, W. C. (1980). *Pharmacology of Neuromuscular Function*, pp. 62, 71, 180. Bristol: John Wright and Sons.

—— Webb, S. N. (1976). Tetanic fade during partial transmission failure produced by non-depolarizing neuromuscular blocking drugs in the cat. *Clin. Exp. Pharmacol. Physiol.*, **3**, 545.

Buzello, W., Bischoff, G., Kuhls, E., and Noldge, G. (1980). The new non-depolarizing muscle relaxant Org NC 45 in clinical anaesthesia: preliminary results. *Br. J. Anaesth.*, **52**, 625.

Colquhonn, D., Dryer, F., and Sheridan, R. E. (1979). The actions of tubocurarine at the frog neuromuscular junction. *J. Physiol. (Lond.)*, **293**, 247.

Crul, J. F., and Booij, L. H. D. J. (1980). First clinical experiences with Org NC 45. *Br. J. Anaesth.*, **52**, 49S.

Del Castillo, J., and Katz, B. (1954). Quantal components of the end-plate potential. *J. Physiol. (Lond.)*, **124**, 560.

Durant, N. N., Marshall, I. G., Savage, D. S., Nelson, D. N., Sleigh, T., and Carlyle, I. C. (1979). The neuromuscular and autonomic blocking activities of pancuronium, Org NC 45 and other pancuronium analogues in the cat. *J. Pharm. Pharmacol.*, **31**, 831.

Elmquist, D., and Josefsson, J. O. (1962). The nature of neuromuscular block produced by neomycine. *Acta Physiol. Scand.*, **54**, 105.

Galindo, A. (1971a). Depolarizing neuromuscular block. *J. Pharmacol. Exp. Ther.*, **178**, 339.

—— (1971b). Prejunctional effect of curare: Its relative importance. *J. Neurophysiol.*, **34**, 289.

—— (1972a). Curare and pancuronium compared: effects on previously undepressed mammalian myoneural junction. *Science*, **178**, 753.

—— (1972b). The role of prejunctional effects in myoneural transmission. *Anesthesiology*, **36**, 598.

—— Kennedy, R. (1974). Further observations on depolarizing neuromuscular block: The so-called phase II block. *Br. J. Anaesth.*, **46**, 405.

Hubbard, J. I., and Wilson, D. F. (1973). Neuromuscular transmission in a mammalian preparation in the absence of blocking drugs and the effect of d-tubocurarine. *J. Physiol. (Lond.)*, **228**, 307.

—— —— Miyamoto, M. (1969). Reduction of transmitter release by d-tubocurarine. *Nature (Lond.)*, **223**, 531.

Jenkinson, D. H. (1960). The antagonism between tubocurarine and substances which depolarize the motor end-plate. *J. Physiol. (Lond.)*, **152**, 309.

Katz, B., and Miledi, R. (1973a). The effect of α bungarotoxin on acetylcholine receptors. *Br. J. Pharmacol.*, **49**, 138.

—— —— (1973b). The binding of acetylcholine to receptors and its removal from the synaptic cleft. *J. Physiol. (Lond.)*, **231**, 549.

—— —— (1978). A re-examination of curare action at the motor end-plate. *Proc. R. Soc. Lond.*, **203**, 119.

Marshall, I. G., Agoston, S., Booij, L. H. D. J., Durant, N. N., and Foldes, F. F. (1980). Pharmacology of Org NC 45 compared with other non-depolarizing neuromuscular blocking drugs. *Br. J. Anaesth.*, **52**, 11S.

Marshall, R. J., McGrath, J. C., Miller, R. D., Docherty, J. R., and Lamar, J. C. (1980). Comparison of the cardiovascular actions of Org NC 45 with those produced by other non-depolarizing neuromuscular blocking agents in experimental animals. *Br. J. Anaesth.*, **52**, 21S.

Miyamoto, M. D. (1978). The actions of cholinergic drugs on motor nerve terminals. *Pharmacol. Rev.*, **29**, 221.

Rang, H. P., and Ritter, J. M. (1970a). On the mechanism of desensitisation at cholinergic receptors. *Mol. Pharmacol.*, **6**, 357.

—— —— (1970b). The relationship between desensitisation and the metaphilic effect at cholinergic receptors. *Mol. Pharmacol.*, **6**, 383.

Ryall, R. W. (1979). *Mechanisms of Drug Action on the Nervous System*, p. 22. Cambridge: Cambridge University Press.

Standaert, F. G. (1964). The action of d-tubocurarine on the motor nerve terminal. *J. Pharmacol. Exp. Ther.*, **143**, 181.

—— Riker, W. F. (1967). The consequences of cholinergic drug actions on motor nerve terminals. *Ann. N.Y. Acad. Sci.*, **144**, 517.

Torda, T. (1980). The nature of gentamycin-induced neuromuscular block. *Br. J. Anaesth.*, **52**, 325.

—— Gage, P. W. (1977). Postsynaptic effect of i.v. anaesthetic agents at the neuromuscular junction. *Br. J. Anaesth.*, **49**, 771.

—— Kiloh, N. (1982). Org NC 45 reduces quantal release of acetylcholine. *Anaesth. Intens. Care*, (in press).

## ACTIONS NEUROMUSCULAIRES DE L'ORG NC 45

### RESUME

Dans la préparation du muscle couturier de crapeau, l'Org NC 45 diminue le contenu élémentaire moyen du potentiel post-jonctionnel dans les préparations traitées au magnésium et aussi dans celles traitées à la tubocurarine, et il bloque les récepteurs post-jonctionnels. A une concentration qui permette l'enregistrement du très faible courante post-jonctionnel, on n'a pas pû retrouver de bloc de canal.

## DIE MYONEURALE WIRKUNG VON ORG NC45

### ZUSAMMENFASSUNG

An einem Präparat aus dem M. sartorius der Kröte setzte Org NC45 den mittleren Quanteninhalt des Endplattenpotentials sowohl in mit Magnesium und Tubokurarin behandelten Präparaten, als auch in den blockierenden postsynaptischen Rezeptoren herab. In einer Konzentration, die die Messung des Miniatur-Endplattenpotentials erlaubt, zeigte sich kein Kanalblock.

## ACCIONES MIONEURALES DEL ORG NC 45

### SUMARIO

En la préparación del sartorio de zapo, el Org NC45 redujo el tenor cuántico medio del potencial de la placa-terminal tanto en la preparación tratada por magnesio como en la tratada por tubocurarina, y también bloqueó los receptores post-juncionales. En una concentración que permita el registro de la corriente miniatura de la placa-terminal, no fue demostrado ningún bloqueo del canal.

*Br. J. Anaesth.* (1982), 54, 1223

# EFFECTS OF INHALATION ANAESTHETIC AGENTS ON THE ELECTRICAL AND MECHANICAL ACTIVITY OF THE RAT DUODENUM

J. W. WRIGHT, T. E. J. HEALY, T. W. BALFOUR AND J. D. HARDCASTLE

## SUMMARY

Sleep doses of halothane (4%), enflurane (2%) and diethyl ether (10%) were administered to fasting rats. Duodenal mechanical and electrical activities were recorded using miniature extraluminal strain gauges and silver/silver chloride bipolar electrodes. Halothane abolished, or significantly reduced, phase III activity of the migrating myo-electric complex whereas enflurane abolished phase II activity but failed to reduce phase III. Ether was associated with periods of intense activity throughout anaesthesia and this activity persisted after recovery of consciousness. All anaesthetic agents caused a marked slowing of the basic electrical rhythm.

There are two components of electrical activity in gastrointestinal smooth muscle, slow waves (basic electrical rhythm (BER)) and spike potentials (fast activity). BER arises from the smooth muscle of the bowel, is myogenic in origin (Prosser and Bortoff, 1968) and is thought to be involved in co-ordination of intestinal motility. Spike potentials only occur superimposed on the slow waves; they are associated with muscular contractions and are directly related to changes in intraluminal pressure (Bass and Wiley, 1965).

Following an intra-abdominal operation, the gastrointestinal tract may remain inactive for a variable period (Neely and Catchpole, 1971). This temporary disturbance of intestinal motor function has been termed "functional" or "physiological" ileus. A disturbance of BER may be responsible for the lack of propulsive movements in the intestine in the period after operation and a normal BER is reliable evidence of the recovery of normal motility (Dauchel et al., 1976). Changes in gastrointestinal motility may result from both the handling of the bowel at operation (Bueno, Ferre and Ruckebusch, 1978) and from the type of anaesthetic agent used (Wakim and Mann, 1943). Chronically implanted extraluminal strain gauges and bipolar needle electrodes have been used to monitor the effects of i.v. anaesthetic agents on canine intestinal activity (Healy et al., 1981). However, there is no recent information about the effects of inhalation anaesthetic agents.

## METHODS

A miniature recording unit consisting of two metal foil strain gauge transducers and two silver/silver chloride bipolar electrodes, enclosed in a protective spring, was constructed (Wright et al., 1981).

Twenty-five male Wistar rats of approximately 250 g weight were premedicated with atropine sulphate 24 $\mu g\,kg^{-1}$ body weight to prevent salivation and then anaesthetized with ether. A midline incision of the abdomen was made together with a longitudinal incision of the skin between the scapulae. The recording units and leadwires were drawn subcutaneously from the shoulder blades into the abdominal cavity and the miniature strain gauges and electrodes were sewn alternately along the duodenum at 1-cm intervals, the first strain gauge being adjacent to the pylorus. The compression spring protecting the leadwires was sewn on to the abdominal muscle. The distal end of the spring terminated in a 10-pin electrical connector embedded in a ball assembly which was free to slide along the bars of a modified cage during normal animal movements.

The electrical and mechanical activities were simultaneously monitored using a six-channel pen recorder (Grass Inst., Quincy, Mass.) in line with a seven-channel instrumentation tape-recorder (Store 7D, Racal Thermionic, Southampton). The taped record allowed data to be subjected to computer analysis and also to be replayed at speeds greater than real time. A spike processor (Digitimer, D139, Welwyn Garden, Herts) was used to distinguish

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between spike potentials and slow waves and these signals, with the mechanical activity signal, were entered into a PDP 11/10 computer (Digital Electronic Corp., Galway, Ireland). Graphic displays of mechanical and electrical activity with time were produced together with a fast fourier frequency analysis of the slow wave electrical and mechanical activity with time. Recordings from the rats were made at intervals immediately after operation and for several weeks following implantation of the electrodes and strain gauges. The rats were housed in metabolism cages to prevent coprophagy and fasted for 18 h before being transferred to a wire bottom Perspex box for the study (fig. 1). Air was supplied to the box under positive pressure and recordings of electrical and mechanical activity were made until at least three migrating myo-electrical complexes (MMC) (Szurszewski, 1969) had passed the recording sites. The MMC can be conveniently divided into three separate phases; phase I consists of slow waves only, phase II has intermittent spike potentials superimposed on BER and phase III consists of a burst of intense electrical activity with spike potentials occurring on each slow wave.

## RESULTS

### *Normal fasting response*

Thirty observations were made in 12 rats. There was no disruption of electrical or mechanical activity when the rat was placed into the Perspex box. In the fasted rat, MMC occurred at intervals of 10.1 min (SD ± 3.31) with phase III activity having a duration of 2.7 min (SD ± 1.08) (fig. 2). The normal BER had a mean frequency of 41.9 cycles per min (SD ± 1.31) but slowed significantly to 37.6 cycles per min (SD ± 1.5) ($t = 18.17$; $P < 0.001$) during phase III of MMC.

Mechanical activity also occurred in a cyclical nature, with muscle contractions correlating well with spike potentials (fig. 2).

### *Effects of enflurane anaesthesia*

Eleven observations were made in 10 rats. A sleep dose of 2% enflurane was associated, within 0.85 min (SD ± 0.37), with a marked increase in both mechanical and electrical activity which was propagated from the proximal strain gauge to the distal electrode (fig. 3). The duration of the spiking activity did not differ significantly from that of phase III of MMC. Throughout the period of anaesthesia, no phase II intermittent spiking activity occurred. The duration of successive MMC was reduced to 8.05 min (SD ± 4.25) ($t = 2.66$; $P < 0.01$), but there was no significant change in duration of phase III activity.

BER slowed to 34.8 cycles per min (SD ± 2.63)

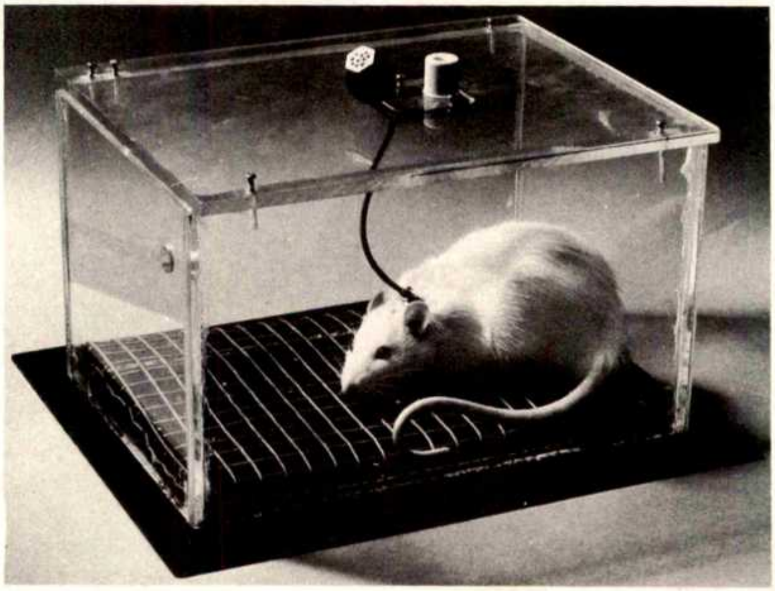

FIG. 1. Rat in the wire bottom Perspex box before anaesthesia. The ball and protective spring arrangement and the 10-pin electrical connector are shown.

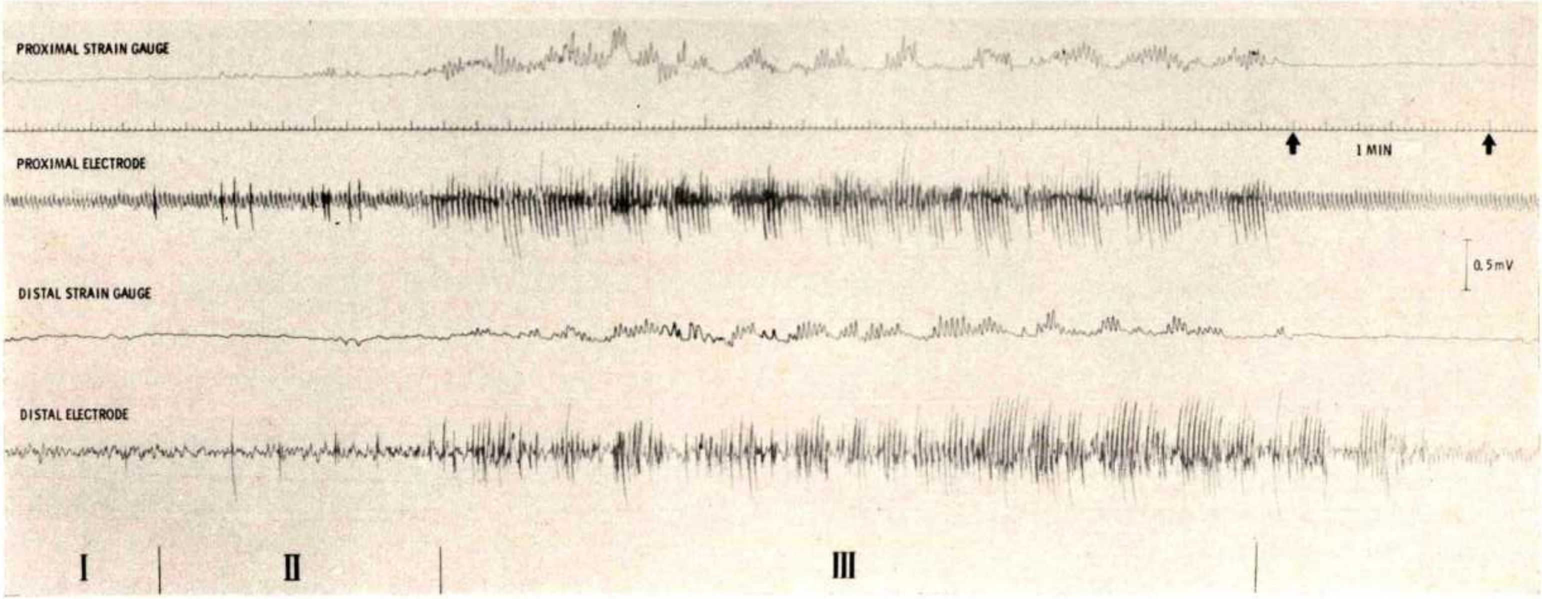

FIG. 2. A normal MMC recorded from the duodenum of a fasted rat. Activity is propagated from the proximal strain gauge to the distal electrode. The three phases of MMC (I, II, III) recorded from the proximal electrode and strain gauge are indicated.

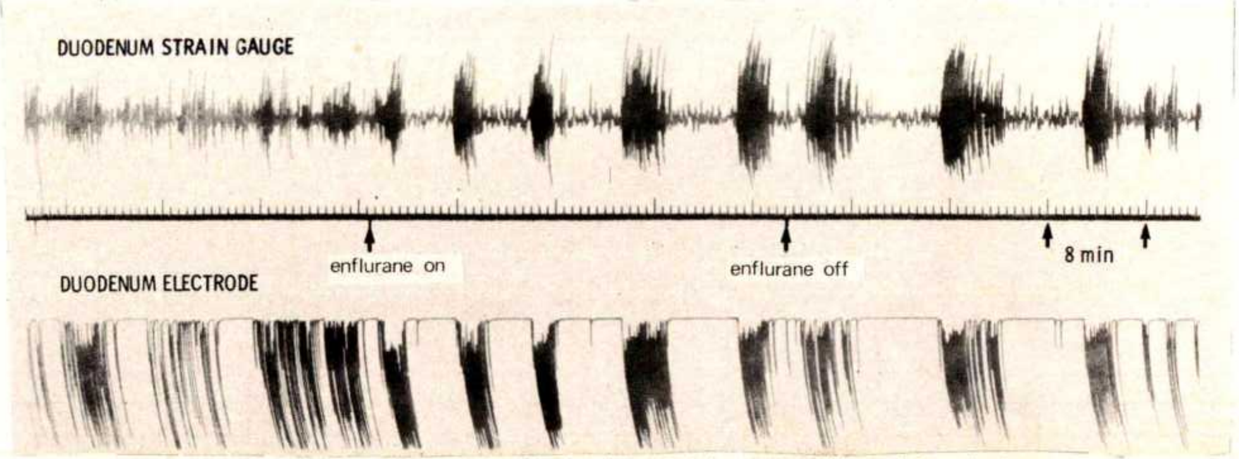

FIG. 3. The effect of enflurane anaesthesia. The electrical record shows only spiking activity—the slow waves have been removed by selective filtering. MMC occur throughout the whole experiment.

($t = 12.56$; $P < 0.001$) during phase I of MMC and to 29.63 cycles per min (SD ± 2.01) ($t = 12.99$; $P < 0.001$) during phase III of MMC (fig. 4A, B). There was no significant difference in the duration of MMC either before anaesthesia or in the recovery period following anaesthesia.

### *Effects of halothane anaesthesia*

Nineteen observations were made in 11 rats. A sleep dose of 4% halothane was associated, within 0.4 min (SD ± 0.25), with a stimulation of both mechanical and electrical activity which was propa-

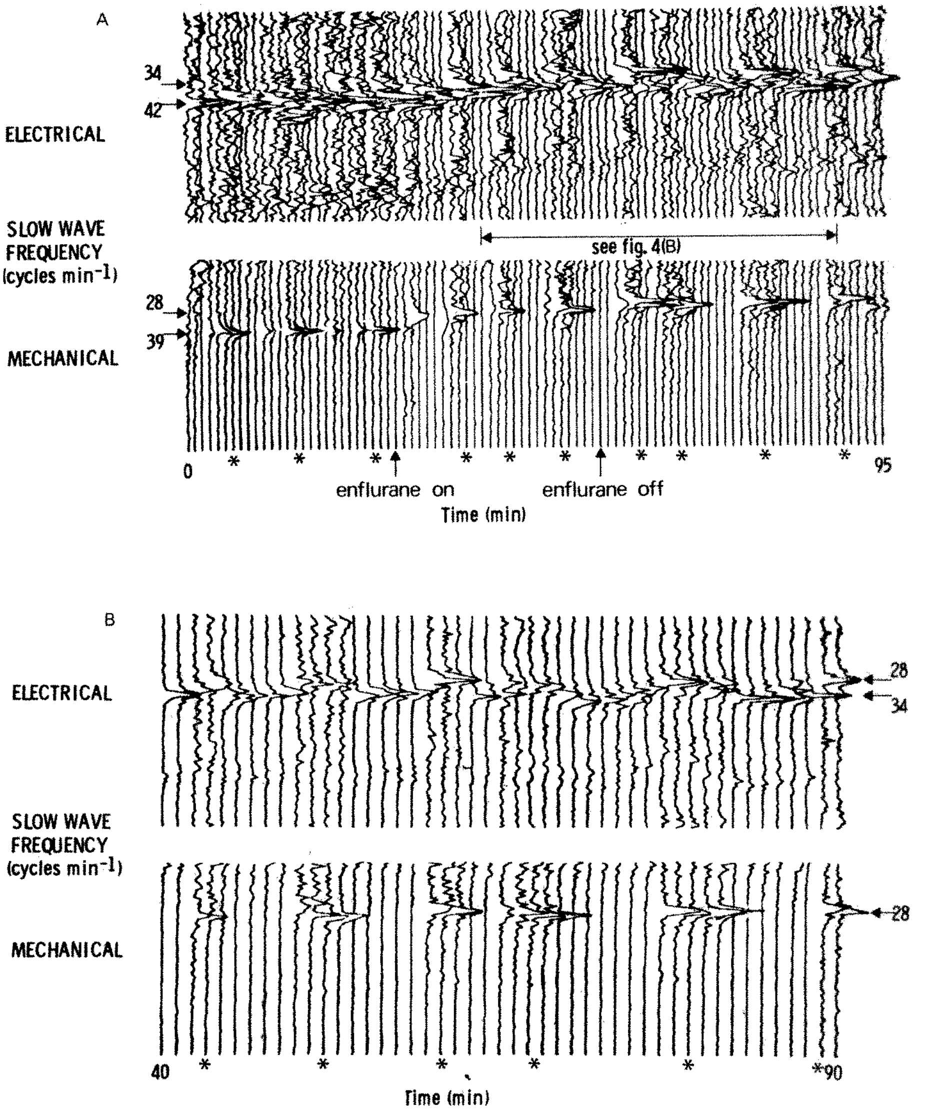

FIG. 4. A: Fast fourier frequency analysis of the BER and of the mechanical activity against time. *Phase III MMC activity. A reduction in frequency occurs in both the electrical (42-34 cycles per min) and mechanical (39-28 cycles per min) records during the period of enflurane anaesthesia. A similar decrease in frequency occurs when halothane or ether is used. B: Fast fourier frequency analysis of BER and mechanical activity against time. The original analysis has been expanded to show the activity occurring between 40 and 90 min after the start of the experiment. Two distinct electrical frequencies (28-34 cycles per min) can be seen, the slower of which corresponds to that occurring during phase III of MMC.

gated distally. The duration of this activity did not differ significantly from that of phase III of the fasting MMC. In all experiments, phase III activity was abolished or significantly reduced ($t = 2.43$; $P < 0.05$) (fig. 5). In 15 experiments there was a significant increase in the duration of MMC interval during anaesthesia ($t = 2.73$; $P < 0.05$). The remaining four experiments had a total MMC duration that was either reduced or unchanged, but all had reduced phase III activity ($t = 2.03$; $P < 0.05$). BER of the duodenum was also significantly reduced to 35.5 cycles per min (SD ± 3.05) ($t = 9.29$; $P < 0.001$) and, in those experiments in which reduced phase III activity occurred, BER of this activity was reduced to 32.7 cycles per min (SD ± 2.67) ($t = 9.103$; $P < 0.001$). After the cessation of anaesthesia, activity returned quickly and initially there was no significant difference between MMC recorded before and after anaesthesia. However, after approximately 30 min, 70% of the rats had the organized activity replaced by sporadic bursts with no recognizable MMC patterns present.

### *Effects of ether anaesthesia*

Twelve observations were made in 10 rats. A sleep dose of 10% ether was associated, within 2.13 min (SD ± 1.98), with an intense stimulation of both mechanical and electrical activity which persisted for several minutes. MMC pattern was totally disrupted during the period of anaesthesia with spike activity occurring on 67.6% (SD ± 20.2) of all slow waves compared with 45.4% (SD ± 39.6) during a control period of 30 min in the pre-anaesthetic stage. Spiking activity further increased after termination of the anaesthetic and, during the first 30 min after anaesthesia, spikes occurred on 87.72% (SD ± 14.35) of all slow waves (fig. 6). The normal MMC pattern did not return for several hours after anaesthesia. During anaesthesia, BER of the duodenum was significantly reduced to 33 cycles per min (SD ± 1.82) ($t = 3.98$; $P < 0.001$).

## DISCUSSION

In the fasted rat, MMC occurs at regular intervals and consists of a band of intense spiking activity which migrates distally from the stomach to the small intestine. As one complex reaches the terminal ileum a new complex begins in the stomach and the cycle restarts (Ruckebusch and Fioramonti, 1975). This migrating wave of contractile activity propels intestinal secretions and cellular debris caudad (Szurszewski, 1969).

In the present study, an initial period of intense activity occurred at the onset of anaesthesia. This activity, which included large slow waves superimposed on the normal BER, was propagated distally and occurred in all animals. The large slow waves were probably gastric in origin since it is known that in some species these can be recorded from proximal small bowel (Bortoff and Davies, 1968). The time taken to achieve surgical anaesthesia varied accord-

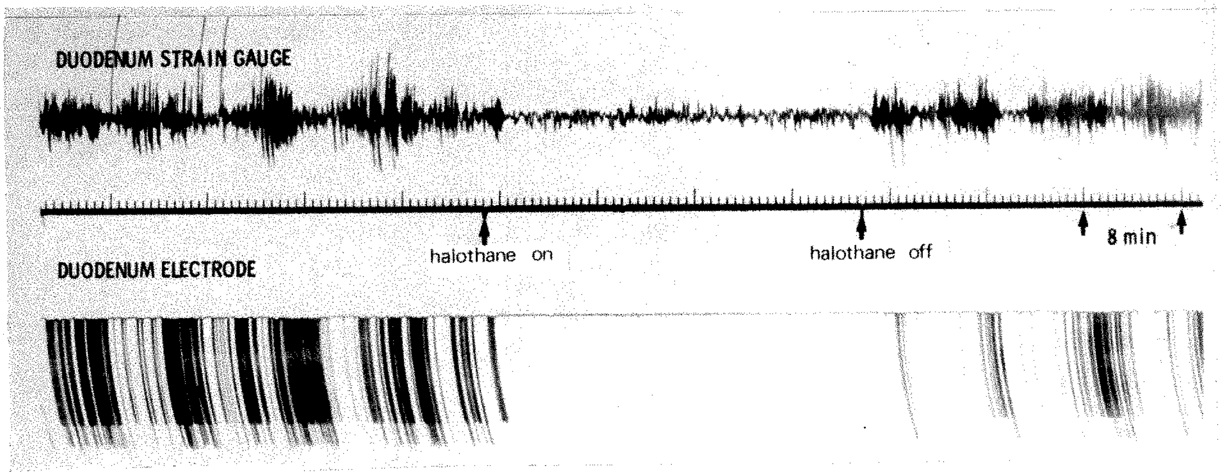

FIG. 5. The effect of halothane anaesthesia. The filtered electrical record shows only the presence of spiking activity. MMC are abolished during anaesthesia and the co-ordinated patterns of activity are disrupted in the recovery stages.

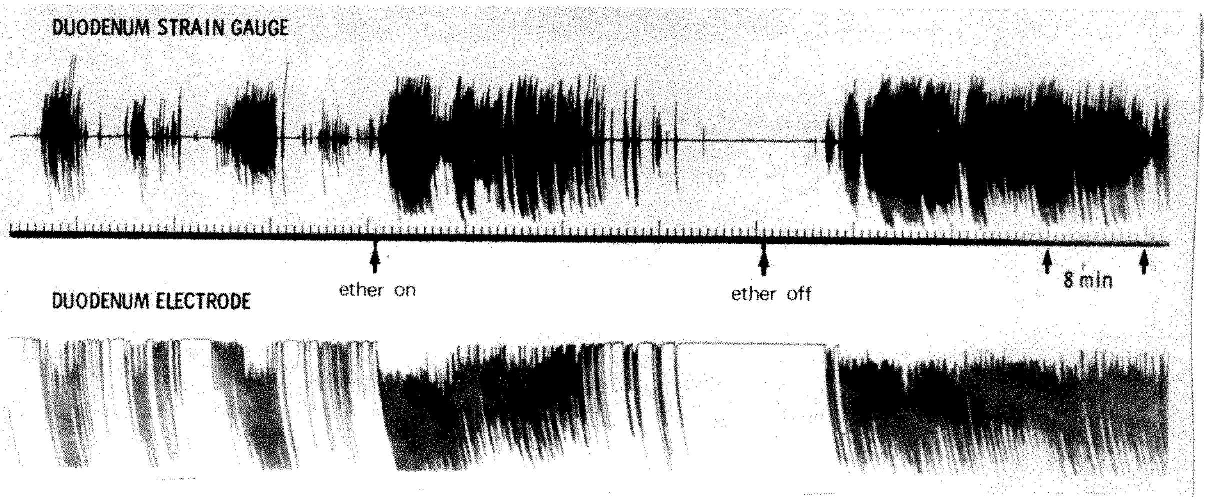

FIG. 6. The effect of ether anaesthesia. The electrical signal has been filtered and spiking activity only is displayed. The co-ordinated MMC activity is replaced by intense spiking at the onset of anaesthesia and this increased activity continues after cessation of anaesthesia.

ing to the anaesthetic agent used, halothane and enflurane having shorter induction times than ether. The onset of the initial spiking also followed a similar pattern, halothane and enflurane producing activity within 0.4 min and 0.58 min respectively and ether within the slower time of 2.13 min. The duration of this activity induced by halothane and enflurane did not differ significantly from phase III of MMC.

Previous studies of the effects of anaesthetic agents on gut motility have shown great variation in both methods and results. A determination of the transit time of a test meal following ether anaesthesia has shown small bowel propulsion to be either significantly delayed (Emerson, 1937; Reynell and Spray, 1957) or to have no effect (Ohrn, Johansson and Nilsson, 1976). Similar conflicting results have been obtained with halothane anaesthesia in dogs. Marshall, Pittinger and Long (1961) reported a depression of motility whereas Smith, Kelly and Weinshilboum (1977) reported no alteration in either the periodicity of MMC or the frequency of the slow waves. Other workers have used balloons to measure intestinal pressure in animals in which Biebl loops of exteriorized gut (Golden and Mann, 1943) and Thiry-vella loops (Bisgard and Johnson, 1939) have been constructed. The use of extraluminal strain gauges and bipolar electrodes has the advantage of allowing both mechanical and electrical activity to be recorded simultaneously while the lumen of the bowel remains free from physical stimuli, and results produced by this method compare favourably with those of other workers (Ruckebusch and Fioramonti, 1975).

Ether totally disrupted MMC patterns of activity during anaesthesia and for several hours afterwards and so it was necessary to analyse these results differently from those of halothane and enflurane. It has been suggested that the duration of anaesthesia has no effect on motility (Golden and Mann, 1943), but we have found that spiking activity tends to become less with increased duration of anaesthesia. The spiking activity which occurred throughout anaesthesia and for some hours afterwards appeared to be unco-ordinated and was not propagated distally. This might account for the lack of propulsion noted by other workers using transit of test meals as an index of motility. Halothane abolished or significantly reduced phase III activity in the duodenum and, in the period after anaesthesia, intestinal motor activity was also significantly slowed. This alteration of MMC would again suggest reduced motility and delayed transit of test meals.

Enflurane did not affect the duration of phase III activity and indeed the frequency of MMC increased throughout anaesthesia, slowing to a normal rate after anaesthesia had been terminated. The MMC were co-ordinated and propagated distally.

The anaesthetic agents halothane, enflurane and ether each have profound but differing effects on gastrointestinal motility. In all experiments, BER was significantly reduced during anaesthesia and normal activity did not return for a considerable period after cessation of anaesthesia. In view of the close relationship between BER and spiking activity, a reduction in the BER may be an important factor in the occurrence of ileus after laparotomy. In the present study, halothane and ether have both been shown to disrupt MMC patterns during and after anaesthesia and this might explain why the transit of test meals has been reduced. Enflurane did not affect the waves of contractile activity passing down the intestine although it did significantly reduce BER. This suggests that the occurrence of ileus is not wholly dependent on the slowing of BER.

The results presented in this study suggest that, of the anaesthetic agents tested, only enflurane is unlikely to contribute to the reduction in intestinal motility which follows operative procedures.

## REFERENCES

Bass, P., and Wiley, J. N. (1965). Electrical and extraluminal contractile-force activity of the duodenum of the dog. *Am. J. Dig. Dis.*, **10**, 183.

Bisgard, J. D., and Johnson, E. K. (1939). The influence of certain drugs and anesthetics upon gastro-intestinal tone and motility. *Ann. Surg.*, **110**, 802.

Bortoff, A., and Davies, R. (1968). Myogenic transmission of antral slow waves across the gastroduodenal junction *in situ*. *Am. J. Physiol.*, **215**, 889.

Bueno, L., Ferre, J. P., and Ruckebusch, Y. (1978). Effects of anaesthesia and surgical procedures on intestinal myoelectric activity in rats. *Dig. Dis.*, **23**, 690.

Dauchel, J., Schang, J. C., Kachelhoffer, J., Eloy, R., and Grenier, J. F. (1976). Gastrointestinal myoelectrical activity during the post-operative period in man. *Digestion*, **14**, 293.

Emerson, G. A. (1937). Intestinal motility in rats anaesthetized with ether. *Am. J. Dig. Dis.*, **4**, 255.

Golden. R. F., and Mann, F. C. (1943). The effects of drugs used in anesthesiology on the tone and motility of the small intestine. An experimental study. *Anesthesiology*, **4**, 577.

Healy, T. E. J., Foster, G. E., Evans, D. F., and Syed, A. (1981). Effect of some i.v. anaesthetic agents on canine gastrointestinal motility. *Br. J. Anaesth.*, **53**, 229.

Marshall, F. N., Pittinger, C. B., and Long, J. P. (1961). Effects of halothane on gastrointestinal motility. *Anesthesiology*, **22**, 363.

Neely, J., and Catchpole, B. (1971). Ileus: The restoration of alimentary tract motility by pharmacological means. *Br. J. Surg.*, **58**, 21.

Ohrn, P. G., Johansson, H., and Nilsson, F. (1976). Influence of ether anaesthesia and oro-gastric intubation on gastric evacuation and small bowel propulsion after laparotomy. *Acta Chir. Scand.* (Suppl.), **461**, 5.

Prosser, C. L., and Bortoff, A. (1968). *Handbook of Physiology*, Section 6, Vol. IV, p. 235. Washington: American Physiological Society.

Reynell, P. C., and Spray, G. H. (1957). The effect of ether and pentobarbitone sodium on gastrointestinal function in the intact rat. *Br. J. Pharmacol.*, **12**, 104.

Ruckebusch, M., and Fioramonti, J. (1975). Electrical spiking activity and propulsion in small intestine in fed and fasted rats. *Gastroenterology*, **68**, 1500.

Smith, J., Kelly, K. A., and Weinshilboum, R. M. (1977). Pathophysiology of postoperative ileus. *Arch Surg.*, **112**, 203.

Szurszewski, J. (1969). A migrating electric complex of the canine small intestine. *Am. J. Physiol.*, **217**, 1757.

Wakim, K. G., and Mann, F. C. (1943). The effects of some intra-abdominal operative procedures on intestinal activity. *Gastroenterology*, **1**, 513.

Wright, J. W., Healy, T. E. J., Balfour, T. W., and Hardcastle, J. D. (1981). A method for long term recording of intestinal mechanical and electrical activity in the unrestrained rat. *J. Pharmacol. Methods*, **6**, 233.

## EFFETS DES AGENTS ANESTHETIQUES PAR INHALATION SUR L'ACTIVITE MECANIQUE ET ELECTRIQUE DU DUODENUM DU RAT

### RESUME

Des doses soporifiques d'halothane (à 4%), d'enflurane (à 3,5%) et d'éther diéthyl (à 10%) ont été administrées à des rats en état de jeûne. Les activités mécaniques et électriques du duodénum ont été enregistrées à l'aide d'indicateurs miniatures de tension extraluminale et des électrodes bipolaires d'argent/chlorure d'argent. L'halothane a aboli ou réduit de manière significative l'activité de la phase III du complexe myo-électrique migrant tandis que l'enflurane éliminait l'activité de la phase II sans réussir à réduire la phase III. Associées à l'éther, des périodes d'activité intense se sont manifestées tout au long de l'anesthésie et cette activité s'est maintenue après la reprise de connaissance. Tous les agents anesthétiques ont provoqué un ralentissement marqué du rythme électrique de base.

## AUSWIRKUNGEN DER INHALIERUNG VON NARKOSEMITTELN AUF DIE ELEKTRISCHEN UND MECHANISCHEN AKTIVITÄTEN DES DUODENUM BEI RATTEN

### ZUSAMMENFASSUNG

Einschläfernde Dosen von Halothan (4%), Enfluran (3,5%) und Diäthyläther (10%) wurden fastenden Ratten verabreicht. Die mechanischen und elektrischen Aktivitäten des Duodenum wurden mittels extraluminaler Miniatur-Dehnungsmesser und Silber/Silberchlorid-Bipolarelektroden gemessen. Durch Halothan wurde die Aktivität in Phase III des wandernde myoelektrischen Komplexes eliminiert oder doch wesentlich reduziert, während Enfluran die Aktivität in Phase II eliminierte, die in Phase II aber nicht reduzieren konnte. Beide Mittel bewirkten Perioden intensiver Aktivität während der gesamten Narkose, und diese Aktivität hielt nach dem Erwachen an. Alle Narkosemittel bewirkten eine deutliche Verlangsamung des grundlegenden elektrischen Rhythmus'.

# EFECTOS DE LOS AGENTES INHALATORIOS ANESTÉTICOS SOBRE LA ACTIVIDAD MECÁNICA Y ELÉCTRICA DEL DUODENO DE RATÓN

## SUMARIO

Se administraron a ratones en ayunas dosis soporíferas de halotano (al 4%), de enflurano (al 3,5%) y éter dietil (al 10%). Se tomó un registro de las actividades mecánicas y eléctricas mediante indicadores miniaturas de tensión extraluminal así como eléctrodos bipolares de plata/cloruro de plata. El halotano eliminó o redujo de manera significante la actividad de la fase III del complejo mio-eléctrico migrante mientras que el enflurano suprimió la actividad de la fase II pero no consiguió reducir la fase III. El éter estuvo asociado con periodos de intensa actividad a todo lo largo de la anestesia y esa actividad persistió después de recobrado el conocimiento. Todos los agentes anestéticos provocaron una disminución marcada del ritmo eléctrico básico.

*Br. J. Anaesth.* (1982), **54**, 1231

# INFLUENCE OF ORAL ATROPINE OR HYOSCINE ON THE ABSORPTION OF ORAL DIAZEPAM

S. M. GREGORETTI AND D. R. A. UGES

SUMMARY

The influence of oral atropine or hysocine on the absorption of oral diazepam administered at the same time was studied in eight volunteers using a three-way crossover randomized double-blind design. No difference was found in the timing of sedation or in the degree of sedation after diazepam alone or in combination with the anticholinergics. Diazepam serum concentrations were not significantly different after the three regimens. It is concluded that the anticholinergics can be given with diazepam for oral premedication without interfering with diazepam absorption.

Diazepam is an effective oral premedicant (Brandt and Oakes, 1965; Moore and Hollis, 1968; Murray, Bechtoldt and Berman, 1968). At times an anticholinergic drug may be required for premedication; indeed this is often a routine practice (Mirakhur et al., 1978). Since both atropine and hyoscine are well absorbed from the gastrointestinal tract, oral administration of the anticholinergic and diazepam together would be convenient. However, anticholinergic compounds may slow the rate of absorption of another drug given orally, by delaying gastric emptying (Nimmo, 1976; Gamble et al., 1976). Delayed absorption could delay the onset of action and this could be detrimental when an immediate effect is required, as when diazepam is given for sedation before the operation.

This study was designed to assess the effects of oral atropine and hyoscine, in doses effective for anticholinergic premedication (Murrin, 1973; Mirakhur, 1978), on the absorption and the clinical effects of oral diazepam.

## METHODS

The study was conducted in eight healthy volunteers, five female and three male, who gave informed consent. Their mean age was 22.7 ± 1.5 yr, body weight 67.4 ± 15.4 kg, and height 1.74 ± 0.14 m. Three of them were smokers who abstained during the experiments and two women were taking oral contraceptives.

The volunteers fasted from midnight for the duration of the experiment. On three occasions, each subject was given orally, with 40 ml of water, one capsule containing diazepam 10 mg, diazepam 10 mg with atropine sulphate 1 mg, or diazepam 10 mg with hyoscine hydrobromide 1 mg. The capsules were prepared to B.P. specifications by our pharmacy. An *in vitro* dissolution test (*British Pharmacopoeia* 1980, vol. II, appendix XII D) did not show any difference in the dissolution rate of diazepam either alone or mixed with the anticholinergics, complete dissolution occurring within 10 min.

The order of drug administration was randomized. The tests were performed always at 8.30 a.m. and a minimum interval of 1 week separated consecutive tests on each subject. The subjects were studied by a single observer (S.M.G.) for 2.5 h after drug administration. During this time the subjects either sat or lay down according to their preference. Sedation was assessed every 15 min following drug administration, using an arbitrary score from 0 (no sedation) to 3 (asleep when left undisturbed), based on both the subject's and observer's evaluation. Other symptoms like dizziness, mouth dryness and blurred vision were also assessed. Neither the subject nor the observer was aware of the nature of the capsule that had been taken.

Venous blood samples for determination of diazepam concentration were taken from an indwelling i.v. cannula before and at 30, 45, 60, 75, 90, 120 and 150 min after drug administration. The serum, separated by centrifugation after clotting, was deep-

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frozen until analysed. Diazepam concentration was determined by high-pressure liquid chromatography according to a general method described elsewhere (van Dijk and Uges, 1980).

The coefficient of variation of the method for diazepam was 4% ($C = 400\,\mu$g litre$^{-1}$, $n = 10$). The correlation coefficient of the calibration curve ($C = 50$–$1000\,\mu$g litre$^{-1}$) was more than 0.999 on each day. Results reported are the mean of duplicate determinations.

Differences were tested using the Wilcoxon matched pairs signed-ranks test and Student's paired *t* test and considered to be significant when $P < 0.05$.

## RESULTS

No difference was found in the time of onset of sedation or in the time of maximum sedation (respectively about 30 min and 60 min) after oral administration of the three preparations. After 60 min, and throughout the observation period, the subjects were more sedated after diazepam and hyoscine than after diazepam alone or with atropine (which were undistinguishable in their effects), although these differences were not statistically significant (fig. 1). Diazepam serum concentrations were not significantly different after diazepam alone or combined with the anticholinergics (fig. 2). All the subjects experienced a dry mouth after the anticholinergics, but none after diazepam alone. This symptom was noted at 60 min, was most marked at 75–90 min, and persisted until the end of the study. No difference was detected between atropine and hyoscine. One subject complained of dizziness during all three tests. No other side-effect was detected. No volunteer judged the subjective feelings after the drug(s) as unpleasant.

## DISCUSSION

In this study, atropine and hyoscine administered with diazepam did not affect the time course of clinical effects or the serum concentrations of diazepam, suggesting that the former drugs did not influence the absorption of the latter. These results contrast with the reduced rate of gastrointestinal absorption of drugs associated with atropine administration reported by previous authors (Gibbons and Lant, 1975; Gamble et al., 1976). Different routes of administration of atropine or different time

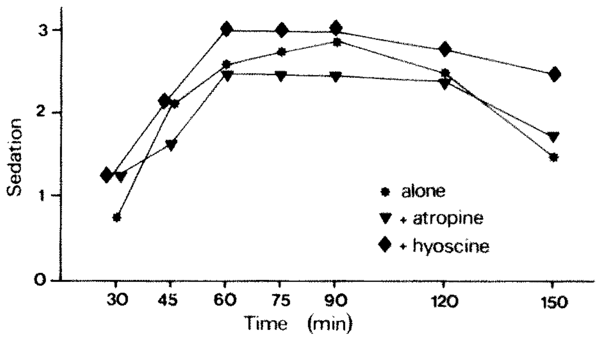

FIG. 1. Mean sedation scores over 150 min following ingestion of diazepam 10 mg, alone or with atropine 1 mg or hyoscine 1 mg.

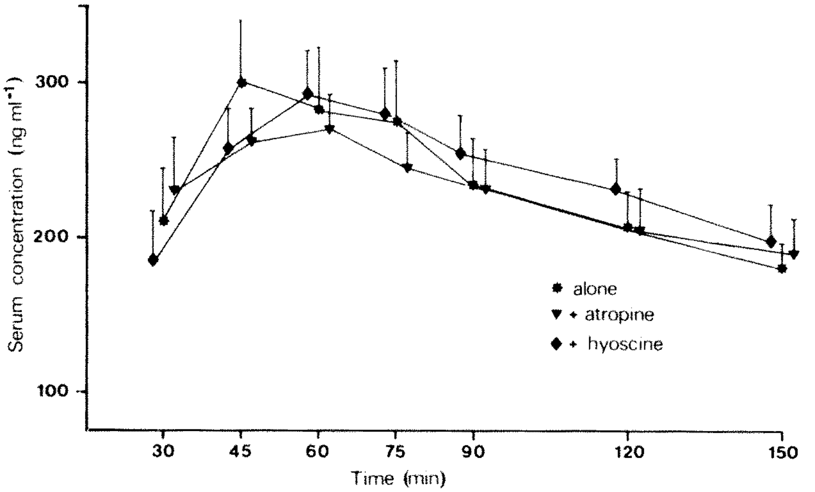

FIG. 2. Mean serum diazepam concentrations over 150 min following ingestion of diazepam 10 mg, alone or with atropine 1 mg or hyoscine 1 mg. Vertical bars represent 1 SEM.

intervals between the administration of atropine and the other drug may explain this discrepancy.

Atropine inhibits gastric motility rapidly after parenteral administration. After an oral dose of atropine the inhibitory effects on gastrointestinal motility develop more slowly and become maximal at 75 min from the start of administration (Chapman, Rowlands and Jones, 1950). This is probably because atropine has to reach the small bowel to be absorbed, as no absorption takes place in the stomach (Beermann, Hellström and Rosén, 1971). No detailed information is available on the effects of hyoscine on gastrointestinal motility.

The speed of effect of parenteral atropine on gastric motility may explain the reduced rate of absorption of diazepam found by Gamble and others (1976) when diazepam was given orally at the same time as parenteral atropine. The reduced absorption of alcohol reported by Gibbons and Lant (1975) may be explained by the fact that the alcohol meal was given 2 h after oral atropine, when stomach motility would be markedly inhibited (Brömster et al., 1969).

In the present study, when the two drugs were administered orally at the same time, both would leave the stomach and reach the absorption sites in the small bowel before any slowing of gastric emptying by atropine might interfere with the transit and hence the absorption of diazepam. It is conceivable that several other drugs with an absorption pattern similar to diazepam could be administered with an anticholinergic without effect on the rate of absorption, provided both drugs are administered orally at the same time. The satisfactory results of combining a sedative–hypnotic drug with an anticholinergic as oral premedication in children (Joseph and Vale, 1960; Doughty, 1962; Gordon and Turner, 1969) support this view. However, drug interactions in gastrointestinal absorption may be very complex, involving several mechanisms, so that the results of this study should be extended to other drugs with caution.

We conclude that, when the use of an anticholinergic is desirable in premedication, atropine or hyoscine can be conveniently administered orally with diazepam (and, probably, similar drugs) without a delay or reduction in its effect.

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## REFERENCES

Beermann, B., Hellström, K., and Rosén, A. (1971). The gastrointestinal absorption of atropine in man. *Clin. Sci.*, **40**, 95.

Brandt, A. L., and Oakes, F. D. (1965). Pre-anesthesia medication: double-blind study of a new drug, diazepam. *Anesth. Analg. (Cleve.)*, **44**, 125.

Brömster, D., Carlberger, G., Lundh, G., Möller, J., and Rosén, A. (1969). The effect of some oral anticholinergics on gastric emptying, pH and osmolarity in man. *Scand. J. Gastroenterol.*, **4**, 185.

Chapman, W. P., Rowlands, P., and Jones, C. M. (1950). Antispasmodic drugs. Evaluation of their effects on the motor activity of the upper portion of the small intestine in man. *J.A.M.A.*, **143**, 627.

Doughty, A. G. (1962). Oral premedication in children. *Br. J. Anaesth.*, **34**, 80.

Dijk, A. van, and Uges, D. R. A. (1980). Analytical and pharmacokinetic aspects of phenobarbital, phenytoin, primidone and carbamazepine; in *The Serum Concentration of Drugs. Clinical Relevance, Theory and Practice*, International Congress Series 501 (ed. F. W. H. M. Merkus), p. 65. Amsterdam: Elsevier-Excerpta Medica.

Gamble, J. A. S., Gaston, J. H., Nair, S. G., and Dundee, J. W. (1976). Some pharmacological factors influencing the absorption of diazepam following oral administration. *Br. J. Anaesth.*, **48**, 1181.

Gibbons, D. O., and Lant, A. F. (1975). Effects of intravenous and oral propantheline and metoclopramide on ethanol absorption. *Clin. Pharmacol. Ther.*, **17**, 578.

Gordon, N. H., and Turner, D. J. (1969). Oral paediatric premedication. *Br. J. Anaesth.*, **41**, 136.

Joseph, M. C., and Vale, R. J. (1960). Premedication with atropine by mouth. *Lancet*, **2**, 1060.

Mirakhur, R. K. (1978). Comparative study of the effects of oral and i.m. atropine and hyoscine in volunteers. *Br. J. Anaesth.*, **50**, 591.

——Clarke, R. S. J., Dundee, J. W., and McDonald, J. R. (1978). Anticholinergic drugs in anaesthesia. A survey of their present position. *Anaesthesia*, **33**, 133.

Moore, P. H., and Hollis, D. A. (1968). Oral premedication with diazepam. *Br. Med. J.*, **2**, 49.

Murray, W. J., Bechtoldt, A. A., and Berman, L. (1968). Efficacy of oral psychosedative drugs for preanesthetic medication. *J.A.MA.*, **203**, 327.

Murrin, K. R. (1973). A study of oral atropine in healthy adult subjects. *Br. J. Anaesth.*, **45**, 475.

Nimmo, W. S. (1976). Drugs, diseases and altered gastric emptying. *Clin. Pharmacokinetics*, **1**, 189.

## INFLUENCE DE L'ATROPINE OU DE LA HYOSCINE PER OS SUR L'ABSORPTION DE DIAZEPAM PER OS

### RESUME

L'influence de l'atropine ou de la hyoscine per os, sur l'absorption du diazépam administré par voie orale en même temps, a été étudiée chez huit volontaires en utilisant un protocole randomisé en double aveugle avec triple croisement. Il n'a pas été trouvé de différences dans la sédation en fonction du temps ni dans le degré de sédation après diazépam seul ou en assocation avec les anticholinergiques. Les concentrations sériques de diazépam n'étaient pas significativement différentes dans les trois pro-

tocoles. Nous en concluons que les anticholinergiques peuvent être administrés avec le diazépam pour une prémédication orale sans interférer avec l'absorption du diazépam.

## DER EINFLUß VON ATROPIN ODER HYOSZYAMIN ORAL AUF DIE ABSORPTION VON ORALEM DIAZEPAM

### ZUSAMMENFASSUNG

Der Einfluß von Atropin oder Hyoszyamin oder Atropin oral auf die Absorption von gleichzeitig verabreichtem oralem Diazepam wurde an acht Freiwilligen untersucht. Das Design war eine dreifach gekreuzte Doppelstudie. Es bestand kein Unterschied im Zeitpunkt der Sedierung oder im Grad der Sedierung nach Diazepam alleine oder zusammen mit den Anticholinergika. Die Diazepam-Serumkonzentrationen unterschieden sich nicht signifikant nach den drei Anwendungsarten. Daraus wird geschlossen, daß die Anticholinergika zusammen mit Diazepam zur oralen Prämedikation ohne Störung der Diazepamabsorption gegeben werden können.

## INFLUENCIA DE LA ATROPINA O HIOSCINA ORAL EN LA ABSORCIÓN DE DIAZEPÁN ORAL

### SUMARIO

Se procedió al estudio de la influencia de la atropina o hioscina oral sobre la absorción del diazepán oral administrados al mismo tiempo en ocho voluntarios mediante el método doble-ciego al azar cruzado y de triple sentido. No se observó diferencia alguna entre el ritmo de sedación o el grado de sedación después de la administración del diazepán sólo o combinado con los anticolinérgicos. Las concentraciones de diazepán en el suero no varíaban de manera significante después de los tres regímenes. Se concluye que pueden administrarse los anticolinérgicos con el diazepán como premedicación oral sin que interfieran con la absorción del diazepan.

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# PARENTERAL RANITIDINE: ONSET AND DURATION OF ACTION

H. G. DAMMANN, P. MÜLLER AND B. SIMON

SUMMARY

Ranitidine 50 mg or an equivalent volume of 0.9% saline were given i.v. to 12 healthy volunteers. pH and volumes of the gastric aspirate were measured at intervals. In all subjects ranitidine provoked a rapid and sustained increase in pH and a concomitant reduction of volume secretion when compared with control.

Pulmonary acid aspiration syndrome has been recognized as a major hazard in the practice of emergency anaesthesia (Edwards et al., 1956; Bannister and Grenvik, 1962). This risk has been associated with a gastric fluid pH of less than 2.5 units (Teaubaut, 1952).

The histamine $H_2$-receptor antagonist cimetidine is likely to be effective in reducing the pulmonary complications following acid aspiration, although this has not been entirely proved (Coombs, Hooper and Colton, 1979; Dobb, Jordan and Williams, 1979).

Recently a new $H_2$-antagonist, ranitidine, has been introduced which is said to be several times more potent, on a molar basis, in inhibiting human gastric acid secretion (Simon et al., 1980; Walt et al., 1981). This study was designed to investigate the onset and duration of action of parenteral ranitidine in healthy volunteers.

## SUBJECTS AND METHODS

Twelve healthy male volunteers (mean age 24, range 20–26 yr) were studied.

After an overnight fast a nasogastric tube was placed in the stomach, the gastric contents were aspirated and the starting pH was determined.

The subjects then received ranitidine 50 mg as an i.v. bolus. In six of them an equal volume of 0.9% saline was given i.v. also, as placebo, in a randomized fashion. Gastric juice was aspirated continuously over a test period of 6 h.

pH of the gastric aspirates was measured using a Radiometer pH electrode and meter. Gastric fluid volumes were collected in 1-h fractions.

This investigation was approved by the medical centre's committee on human experimentation and all subjects gave their written consent.

Statistical analyses were made using the Wilcoxon-test.

## RESULTS

pH of gastric aspirate before administration of ranitidine and placebo (0.9% saline) was about 1.9 (range 1.60–2.60).

Ranitidine as a single bolus injection of 50 mg induced a rapid increase in gastric pH. Forty-five minutes after ranitidine all 12 subjects had a gastric aspirate pH of more than 5 remaining at this value over the whole test period (fig. 1) ($P < 0.05$). By contrast, in the six controls the pH values ranged between 1.30 and 1.90 over the whole 6-h test period.

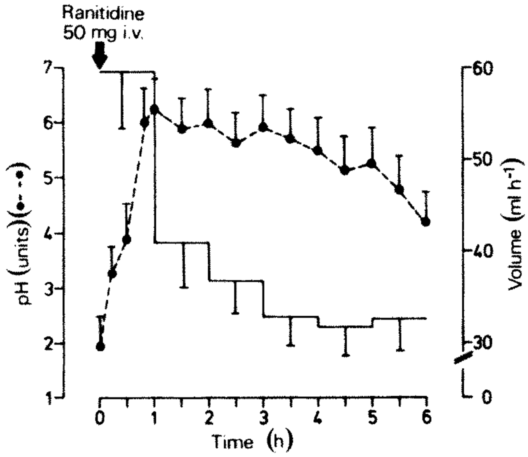

FIG. 1. Effect of ranitidine 50 mg i.v. on the pH and volume of gastric aspirate in 12 healthy volunteers during a 6-h test period (mean values ± SEM).

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Gastric volume secretion in the ranitidine experiments was reduced from 60 ml h$^{-1}$ in the first period of collection to volumes less than 35 ml h$^{-1}$ (45–50% inhibition). In the six volunteers receiving placebo, volume secretion remained considerable (first hour of collection: 67.3 ± 5.8 ml; third hour of collection: 68.4 ± 6.2 ml; sixth hour of collection: 49.6 ± 4.8 ml (± SEM) ($P < 0.05$).

Administration of ranitidine was well tolerated and no complication was discerned.

## DISCUSSION

Our data show that ranitidine 50 mg as an i.v. bolus induces an immediate increase (within 30 min) in gastric aspirate pH and a concomitant marked reduction of volume secretion in each subject. This rapid onset of action would allow a short time interval between administration of this H$_2$-blocker and induction of anaesthesia.

The prolonged activity of ranitidine (more than 6 h) indicates that, at the time of extubation, even after prolonged procedures, the pH of gastric contents would still be high.

In addition to its inhibitory effects on gastric acid secretion, parenteral ranitidine increases the tone of the lower oesophageal sphincter in man (Bertaccini et al., 1981). This may be of further benefit in patients at risk from acid-induced pulmonary damage.

Ranitidine, unlike cimetidine, does not inhibit hepatic drug metabolism (Simon, Müller and Dammann, 1981; Knodell et al., 1982) which is of clinical importance especially in critically elderly patients receiving a large number of drugs.

## REFERENCES

Bannister, W. K., and Grenvik, A. (1962). Vomiting and aspiration during anesthesia. *Anesthesiology*, **23**, 251.

Bertaccini, G., Molina, E., Bobbio, P., and Foggi, E. (1981). Ranitidine increases lower esophageal sphincter pressure in man. *Ital. J. Gastroenterol.*, **13**, 147.

Coombs, D. W., Hooper, D., and Colton, T. (1979). Acid-aspiration prophylaxis by use of preoperative oral administration of cimetidine. *Anethesiology*, **51**, 352.

Dobb, G., Jordan, M. J., and Williams, J. G. (1979). Cimetidine in the prevention of the pulmonary acid aspiration (Mendelson's) syndrome. *Br. J. Anaesth.*, **51**, 967.

Edwards, G., Morton, J. H. V., Pask, E. A. and Wylie, W. D. (1956). Deaths associated with anaesthesia: a report of 1000 cases. *Anaesthesia*, **11**, 194.

Knodell, R. G., Holtzman, J. L., Crankshaw, D. L., Steele, N. M., and Stanley, L. N. (1982). Drug metabolism by rat and human hepatic microsomes in response to interactions with H$_2$-receptor antagonists. *Gastroenterology*, **82**, 84.

Simon, B., Dammann, H. G., Müller, P., and Kather, H. (1980). Ranitidin, ein neu entwickelter Histamin H$_2$-Rezeptor Antagonist. *Dtsch. Med. Wochenschr.*, **105**, 1753.

—— Müller, P., and Dammann, H. G. (1981). H$_2$-Rezeptor-Antagonisten: Vergleichsstudie über Nebenwirkungen und Verträglichkeit. *Diagnost. Intensivmed.*, **6**, 414.

Teaubaut, J. R. (1952). Aspiration of gastric contents: an experimental study. *Am. J. Pathol.*, **28**, 51.

Walt, R. P., Male, P. J., Rawlings, J., Hunt, R. H., Milton-Thompson, G. J., and Misiewicz, J. J. (1981). Comparison of the effects of ranitidine, cimetidine and placebo on the 24-hour intragastric acidity and nocturnal acid secretion in patients with duodenal ulcer. *Gut*, **22**, 49.

## LA RANITIDINE PAR VOIE PARENTERALE: DEBUT ET DUREE DE L'ACTION

### RESUME

Douze volontaires bien portants ont réçu 50 mg de ranitidine ou un volume équivalent de chlorure de sodium à 9% par voie intraveineuse. Le pH et le volume du liquide gastrique aspiré ont été mesurés à intervalles réguliers. Chez tous les sujets, la ranitidine a provoqué une augmentation rapide et soutenue du pH et une baisse concomitante du volume sécrété par rapport au groupe témoin.

## RANITIDIN PARENTERAL: WIRKUNGSBEGINN UND -DAUER

### ZUSAMMENFASSUNG

Ranitidin 50 mg oder eine äquivalente Menge 0,9% Kochsalzlösung wurde zwölf gesunden Freiwilligen verabreicht. Der pH und die Menge des Magenaspirates wurden in Intervallen bestimmt. Bei allen Personen rief Ranitidin einen schnellen und anhaltenden Anstieg des pH und eine gleichzeitige Verminderung des Sekretions-volumens im Vergleich zur Kontrollgruppe hervor.

## RANITIDINA PARENTÉRICA: INICIO Y DURACIÓN DE SU ACCIÓN

### SUMARIO

Se administró 50 mg de ranitidina i.v. o un volumen equivalente de solución salina al 0,9% i.v. a 12 voluntarios sanos. Se midieron el pH y los volúmenes del aspirado gástrico en varios intervalos. En todos los sujetos, la ranitidina provocó un aumento rápido y sostenido del pH y una reducción concomitante de la secreción volumétrica en comparación con los controles.

*Br. J. Anaesth.* (1982), **54**, 1237

# CORRESPONDENCE

## CLODANOLENE SODIUM AND MALIGNANT HYPERPYREXIA

Sir,—We wish to report the results of *in vitro* experiments which examined the effects of clodanolene sodium on muscle contracture in swine which were susceptible to malignant hyperpyrexia (MH). Clodanolene sodium is a skeletal muscle contraction antagonist, closely related to dantrolene sodium.

Susceptibility to MH was identified in seven swine by demonstrating increased sensitivity of their muscle to 3% halothane, caffeine 2 mmol litre$^{-1}$, suxamethonium chloride (Wellcome) 1 mmol litre$^{-1}$ and potassium chloride 80 mmol litre$^{-1}$. The effectiveness of dantrolene sodium 3 μmol litre$^{-1}$ and clodanolene sodium 3 μmol litre$^{-1}$ in inhibiting or reversing the drug-induced contractures was assessed. The effects of dantrolene sodium and clodanolene sodium on isometric twitch were also examined in a range of concentrations from 3 to 30 μmol litre$^{-1}$.

Dantrolene sodium and clodanolene sodium were equally effective in inhibiting and reversing contractures induced by 3% halothane, caffeine 2 mmol litre$^{-1}$ and suxamethonium chloride 1 mmol litre$^{-1}$. Dantrolene sodium had a significantly greater inhibitory effect on contractures induced by potassium chloride 80 mmol litre$^{-1}$ than clodanolene sodium ($P < 0.025$, $n = 7$, Student's *t* test). Dantrolene sodium also had a significantly greater effect than clodanolene sodium on isometric twitch at concentrations of 3 μmol litre$^{-1}$ ($P < 0.01$, $n = 5$), 15 μmol litre$^{-1}$ ($P < 0.01$, $n = 5$) and 30 μmol litre$^{-1}$ ($P < 0.05$, $n = 5$). The difference between the effects of the two drugs at a concentration of 6 μmol litre$^{-1}$ was not statistically significant.

Both dantrolene sodium and clodanolene sodium act at the level of excitation–contraction coupling in muscle (Ellis and Wessels, 1978). The differences reported here between the effect of dantrolene sodium and clodanolene sodium on potassium-induced contractures and isometric twitch in MH muscle, show that subtle differences in drug structure may have significant effects on the ability of skeletal muscle contraction antagonist drugs to inhibit the increased muscle contractility in MH. The results also suggest that clodanolene sodium has no advantage over dantrolene sodium in the treatment or prevention of MH.

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### ACKNOWLEDGEMENT

We are indebted to Dr K. O. Ellis of Norwich-Eaton Pharmaceuticals for supplying us with dantrolene sodium and clodanolene sodium.

### REFERENCE

Ellis, K. O., and Wessels, F. L. (1978). The pharmacology of clodanolene sodium, a new skeletal muscle contraction antagonist. *Arzneim-Forsch. Drug Res.*, **28**, 1100.

## SUPRAVENTRICULAR TACHYCARDIA FOLLOWING PANCURONIUM

Sir,—We read with interest the correspondence by Saemund and Dalenius (1981) on Pancuronium and nodal rhythm. We report here a patient who developed supraventricular tachycardia following pancuronium. This male patient, aged 50 yr, was hypertensive and diabetic, with e.c.g. evidence of complete right bundle right bundle branch block and was operated on for closure of bronchopleural fistula. He had bilateral pneumonitis leading to postoperative ventilatory insufficiency on the 3rd day after operation. He was given diazepam 10 mg i.v. and put on Bird Ventilator and was given pancuronium 4 mg i.v. to control the ventilation. Immediately after i.v. administration of pancuronium the patient developed tachycardia with a heart rate of 180 beat min$^{-1}$ and arterial pressure 200/100 mm Hg. The oscilloscope showed evidence of supraventricular tachycardia which persisted. An e.c.g. was recorded and the patient was given lignocaine hydrochloride 200 mg in two divided doses i.v. and digoxin 0.25 mg i.v. without any change in rhythm. After 10 min verapamil 4 mg i.v. reverted the rhythm to sinus tachycardia with heart rate of 140 beat min$^{-1}$. Repeat e.c.g. after control of arrhythmia failed to show any evidence of myocardial ischaemia, thus ruling out the possibility of ischaemia-induced arrhythmia.

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### REFERENCE

Saemund, O., and Dalenius, E. (1981). Pancuronium and nodal rhythm. *Br. J. Anaesth.*, **53**, 780.

## ACCIDENTAL HIGH-DOSE EXTRADURAL MORPHINE

Sir,—Long-term use of extradural morphine in reducing chronic pain has been used for home care (Zenz et al., 1981). The possibility of misadministration and the risks of side-effects will increase under these circumstances. During a 6-month period, home treatment with extradural morphine was performed on a 61-year-old man suffering from painful metastases secondary to hypernephroma. During the period of treatment the dose of morphine was increased gradually to 6 mg diluted in 15 ml of isotonic saline given extradurally in the lumbar region four times daily. The extradural injections were given by the patient's wife.

Because of still insufficient pain relief a small increase in the daily dose was intended, but by mistake the wife injected morphine chloride 16 mg extradurally five times daily on 2 days (that is 160 mg within 48 h).

Four hours after the last morphine dose the patient was in his usual bad general condition; respiration was unaffected, but catatonic twitchings in his extremities developed. The concentration of free morphine in serum and cerebrospinal fluid (c.s.f.) was at this time 62 nmol litre$^{-1}$ and 10.9 nmol litre$^{-1}$ respectively, measured by a radioimmunoassay technique (Abuscreen).

Concentrations in serum and in c.s.f. present considerable interindividual variations some hours after extradural morphine injections (Jørgensen, Andersen and Engquist, 1981; Weddel and Ritter, 1981). The concentrations of morphine in our patient were within the limits of variations and had probably been larger before the concentrations had been determined, as maximum values for both probably will be reached earlier than 4 h after the injection (Magora et al., 1980; Weddel and Ritter, 1981; Møller et al., 1982).

Tolerance is probably developed in long-term treatment with extradural morphine, so that even large doses of morphine can be tolerated without adverse side-effects. However, extradural morphine administration by unskilled persons might prove hazardous.

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### REFERENCES

Jørgensen, B. C., Andersen, H. B., and Engquist, A. (1981). CSF and plasma morphine after epidural and intrathecal application. *Anesthesiology*, 55, 714.

Magora, F., Olshwang, D., Eimeri, D., Shorr, J., Katzenelson, R., Cotev, S., and Davidson, J. T. (1981). Observations on extradural morphine analgesia in various pain conditions. *Br. J. Anaesth.*, 52, 247.

Møller, I. W., Vester-Andersen, T., Steentoft, A., Hjortsø, E., and Lunding, M. (1982). Respiratory depression and morphine concentration in serum after epidural and intramuscular administration of morphine. *Acta Anaesthesiol. Scand.*, (in press).

Weddel, S. J., and Ritter, R. R. (1981). Serum levels following epidural administration of morphine and correlation with relief of postsurgical pain. *Anesthesiology*, 54, 210.

Zenz, M., Scappler-Scheele, B., Neuhaus, R., Piepenbrock, S., and Hilfrich, J. (1981). Long-term peridural morphine analgesia in cancer pain. *Lancet*, 1, 91.

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## NITROUS OXIDE IN OXYGEN AND TRACHEAL TUBE CUFF VOLUMES

Sir,—In this very interesting article, Mehta (1981) demonstrates that the increase of cuff pressure because of nitrous oxide diffusion is a phenomenon that has to be considered even during brief anaesthesia. He showed that the volume in low pressure-cuffs had almost doubled after 3 h. These results correspond with our own investigations when we found the main increase in cuff pressure to be during the first hours of anaesthesia (Brandt, Pokar and Renz, 1980; Brandt, Beck et al., 1981).

It seems to be important to make some remarks on the following point: Dr Mehta cites Stanley (1975), who asserted that there was a smaller increase in cuff volume and cuff pressure *in vivo* than *in vitro*. He explained this by the smaller diffusion area *in vivo*. In our own studies, pressure and volume were increased *in vivo* just as *in vitro* (Brandt, Pokar and Renz, 1980).

Therefore we questioned the theory of Stanley that only the distal portion of the cuff, that is, the portion not in contact with the tracheal wall, should be the area of diffusion. Our experience indicates that, *in vivo*, the contact area with the tracheal wall is a diffusion area also. This theory can be proved by analysing the cuff pressure curve during operations with extracorporeal circulation (ECC). An example is shown in figure 1.

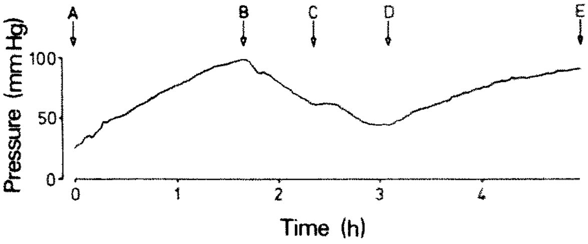

FIG. 1. The pressure in a high volume–low pressure tracheal tube cuff during an operation with extracorporeal circulation (Rüsch Super Safety Cuff, 8.0 mm i.d., $F\mathrm{I}_{\mathrm{N_2O}} = 0.66$). A = after intubation, cuff pressure 24 mm Hg; B = onset of bypass, cuff pressure 98 mm Hg; C = beginning of rewarming the patient; D = termination of ECC, cuff pressure 44 mm Hg; E = end of anaesthesia, cuff pressure 90 mm Hg.

Immediately after intubation (A) the cuff pressure was 24 mm Hg. Until the onset of ECC (B) it increased to 98 mm Hg within 95 min. During the whole time of ECC the pressure decreased discontinuously by 54 mm Hg (D—end of ECC). This pressure reduction occurred in spite of continuing the tracheal ventilation during ECC with 1 litre min$^{-1}$ of the same anaesthetic gas mixture as before ECC ($F\mathrm{I}_{\mathrm{N_2O}}$ 0.66). This ensured that partial pressure relations of the gases were kept constant at the distal cuff area. Nevertheless, the cuff pressure decreased. This pressure decrease during ECC can only occur if nitrous oxide diffuses out of the cuff through the contact area with the tracheal wall additionally. Partial pressure relations changed in this area only: the tracheal tissue becomes free of nitrous oxide during ECC. After termination of ECC (D) the conditions become the same as before ECC. Cuff pressure increases again to nearly the same value of 90 mm Hg until the end of anaesthesia (E).

Therefore, in our opinion, the whole cuff wall constitutes a diffusion area for nitrous oxide *in vivo* (Brandt, Gümrükcü et al., 1981). Moreover, as the size of the contact area is about 10 times the cuff area not in contact with the tracheal wall, the main part of diffusion takes place from tracheal tissue through the contact area into the tracheal cuff, and *vice versa*.

L. BRANDT
*Hamburg*

### REFERENCES

Brandt, L., Beck, H., Pokar, H., and Renz, D. (1981). Die Wahl des Endotrachealtubus zur Narkose-vergleichende Untersuchungen verschiedener Niederdruckmanschettentuben. 17th Central European Congress of Anaesthesiology, Berlin 1981, G 8.8, 195.

——Gümrükcü, V., Pokar, H., and Renz, D. (1981). Lachgasdiffusion in den Tubuscuff—Grundsätzliche Gesichtspunkte. 17th Central European Congress of Anaesthesiology, Berlin 1981, H 1.11, 361.

——Pokar, H., and Renz, D. (1980). Gas-diffusion induced pressure kinetics in low pressure cuffs. Continuous pressure

measurement *in vivo* and *in vitro*. ***Anaesthesist***, **30**, 200.
Mehta, S. (1981). Effects of nitrous oxide and oxygen on tracheal tube cuff gas volumes. ***Br. J. Anaesth.***, **53**, 1227.
Stanley, T. H. (1975). Nitrous oxide and pressures and volumes of high- and low-pressure endotracheal-tube cuffs in intubated patients. ***Anesthesiology***, **42**, 637.

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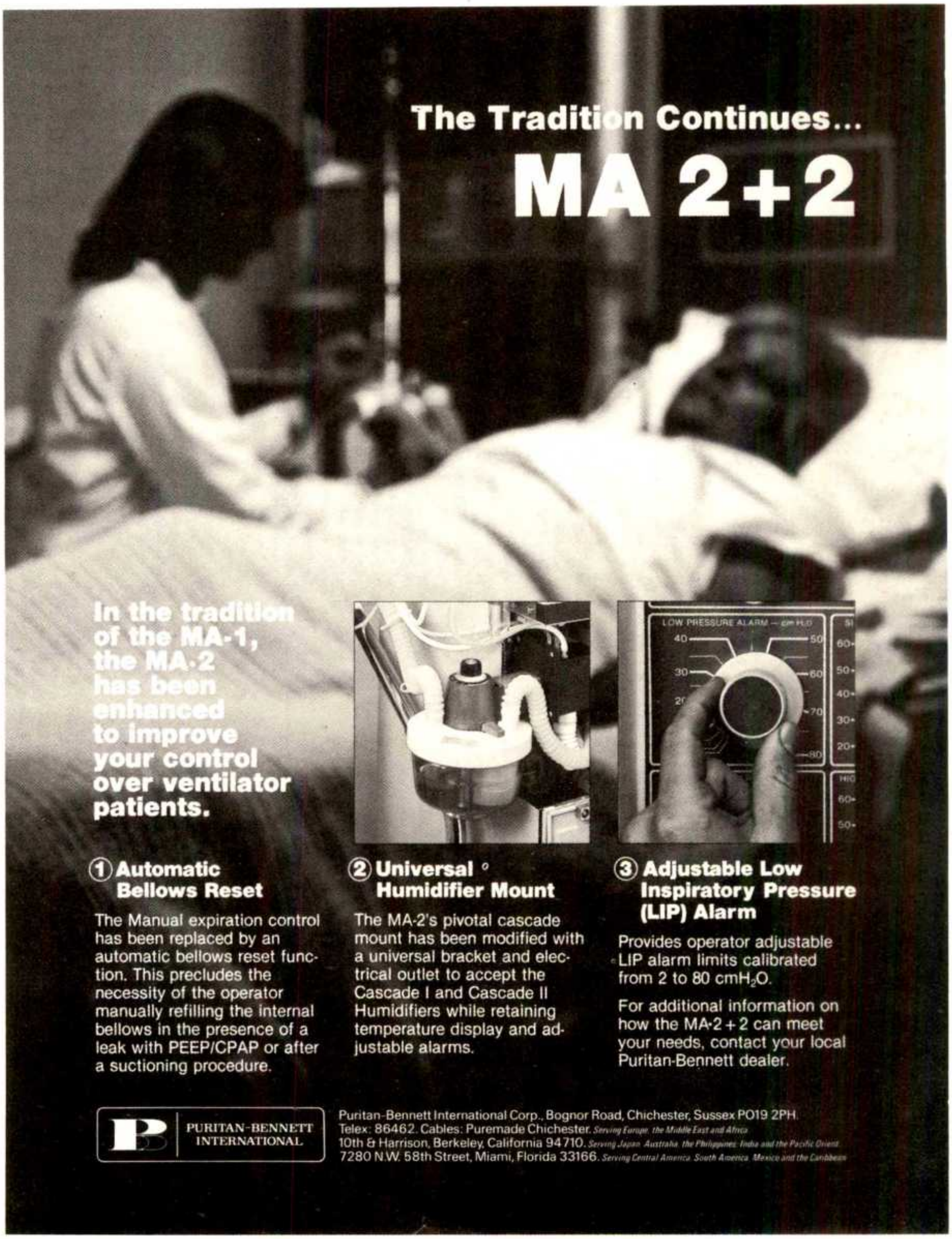

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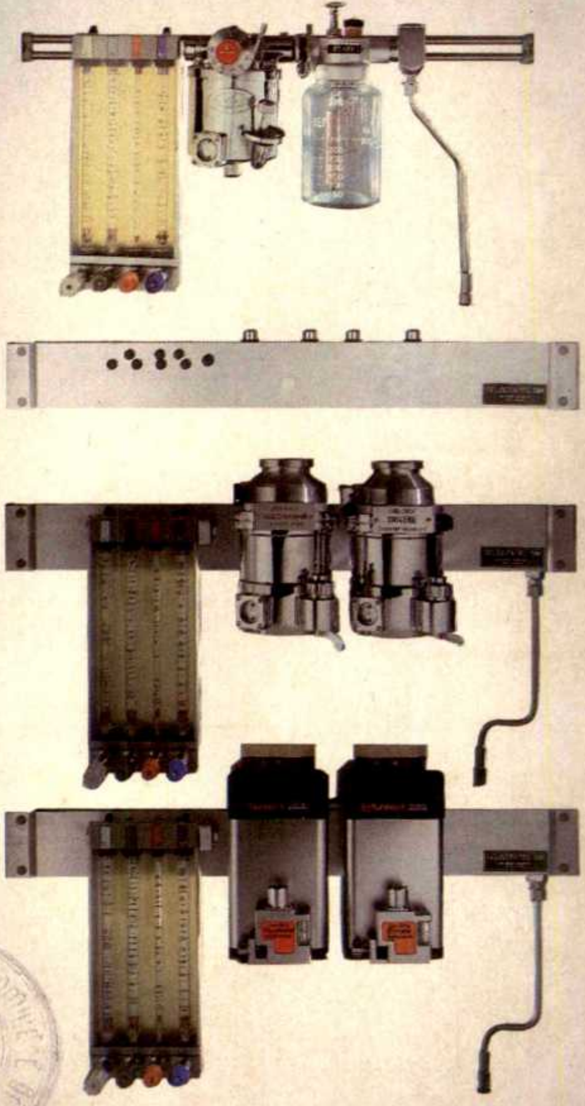

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Anaesthetists
Information
Service

# Balanced anaesthesia?

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Sublimaze* (fentanyl) offers rapid onset of action, a wide safety margin and predictable duration of effect from a single injection – providing profound analgesia both during and after surgery.

Sleep, muscle relaxation and analgesia – the cornerstones of balanced anaesthesia.

TRADEMARK
**SUBLIMAZE**
**fentanyl**
**the versatile analgesic.**

**PRESCRIBING INFORMATION**
**Uses** Low doses for analgesia in short surgical procedures. Higher doses as analgesic/respiratory depressant with assisted ventilation. With a neuroleptic, in neuroleptanalgesia.
**Dosage and Administration** Sublimaze* by the intravenous route may be administered to adults and children as follows:-
**Spontaneous respiration:** adults: 50-200µg then 50µg as required. Children: 3-5µg/kg then 1µg/kg as required.
**Assisted ventilation:** adults: 300-3500µg then 100-200µg as required. Children: 15-50µg/kg then 1-3µg/kg as required. Doses over 200µg are for use only in anaesthesia. As a premedicant, 50-100µg Sublimaze* may be given intramuscularly 45 minutes before induction of anaesthesia.
**Contra-indications** Respiratory depression; obstructive airways disease. Concurrent administration with MAOIs or within 2 weeks of discontinuation of them.
**Warnings** A transient fall in blood pressure may occur after i.v. administration of Sublimaze*.
**Side effects/Overdosage** Doses over 200µg cause significant respiratory depression; reversed by naloxone 0.1-0.2mg. Bradycardia may be antagonised by atropine; muscular rigidity by muscle relaxants. An additive effect may be seen with concomitant use of other narcotics or CNS depressant drugs. Nausea, vomiting, tolerance and dependence may occur.
**Precautions** Myasthenia gravis. Reduce dosage in the elderly, hypothyroidism and chronic hepatic disease. Use in labour may cause respiratory depression in the neonat
**Pregnancy** Little human evidence, no adverse animal effects.
**Legal category** POM MDA
**PL No.** 0242/5001 R
**Package quantities** Sublimaze* is supplied in 2 ml or 10 ml ampoules in packs of 10. Each ml contains 0.05mg fentanyl.
**Basic NHS cost** 2 ml x 10 £4.13. 10 ml x 10 £17.03.

*Sublimaze is a registered trademark.

For further information contact:
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**Janssen Pharmaceutical Limited,**
Janssen House,
Chapel Street,
Marlow,
Bucks.

**cribing information**
gesic Injection 0.3mg/ml buprenorphine, as the
ochloride, ampoules of 1ml (0.3mg) or 2ml (0.6mg).
gesic Sublingual tablet containing 0.2mg buprenorphine,
e hydrochloride. **Uses:** As a strong analgesic for the relief
oderate to severe pain. **Dosage and Administration:**
gesic Injection: Adults: 1-2ml (0.3-0.6mg) by i.m or
i.v. injection, every six to eight hours or as required.
gesic Sublingual: 1-2 tablets
-0.4mg buprenorphine)
olved under the
jue, every 6 to 8
rs or as required.
tablet should not be
wed or swallowed.
gesic is not at
sent recommended
children.
**tra-Indications,**
**nings, etc:** There
no absolute contra-
cations for
gesic. However,
should be taken
en treating patients
impaired
piratory function
emgesic may
equently affect

respiration. Because buprenorphine has antagonist properties, it may precipitate mild withdrawal symptoms in narcotic addicts, and it should be given with care initially to patients previously treated with narcotic analgesics. Temgesic may cause some drowsiness; this could be potentiated by other centrally-acting agents, including alcohol. Ambulent patients should be warned not to drive or operate machinery if affected. Since buprenorphine is metabolised in the liver, the intensity and duration of its action may be affected in patients with impaired liver function. Until further information is available, Temgesic should be used with caution in patients receiving monoamine oxidase inhibitors, and it is not recommended for use during pregnancy. **Side Effects:** Drowsiness is the most common side effect. In common with other strong analgesics, nausea, vomiting, dizziness and sweating have been reported and may be more frequent in ambulant patients. Clinically significant respiratory depression has been observed rarely and only in the post-operative period. **Product Licence Numbers, NHS Price:** at January 1982. Temgesic injection 1ml—44/0056. £5.52/pack 10 ampoules. Temgesic injection 2ml—44/0057. £9.89/pack 10 ampoules. Temgesic Sublingual PL44/0063. £6.00/pack 50 tablets. Irish Product Authorisation Nos. 1ml—PA27/3/1: 2ml—27/3/2. Temgesic Sublingual No. PA27/3/3. Additional information available on request from: Reckitt & Colman Pharmaceutical Division, Hull HU8 7DS.

The Temgesic Post-operative Calendar
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with Temgesic Injection, followed by Temgesic Sublingual 6-8 hourly.
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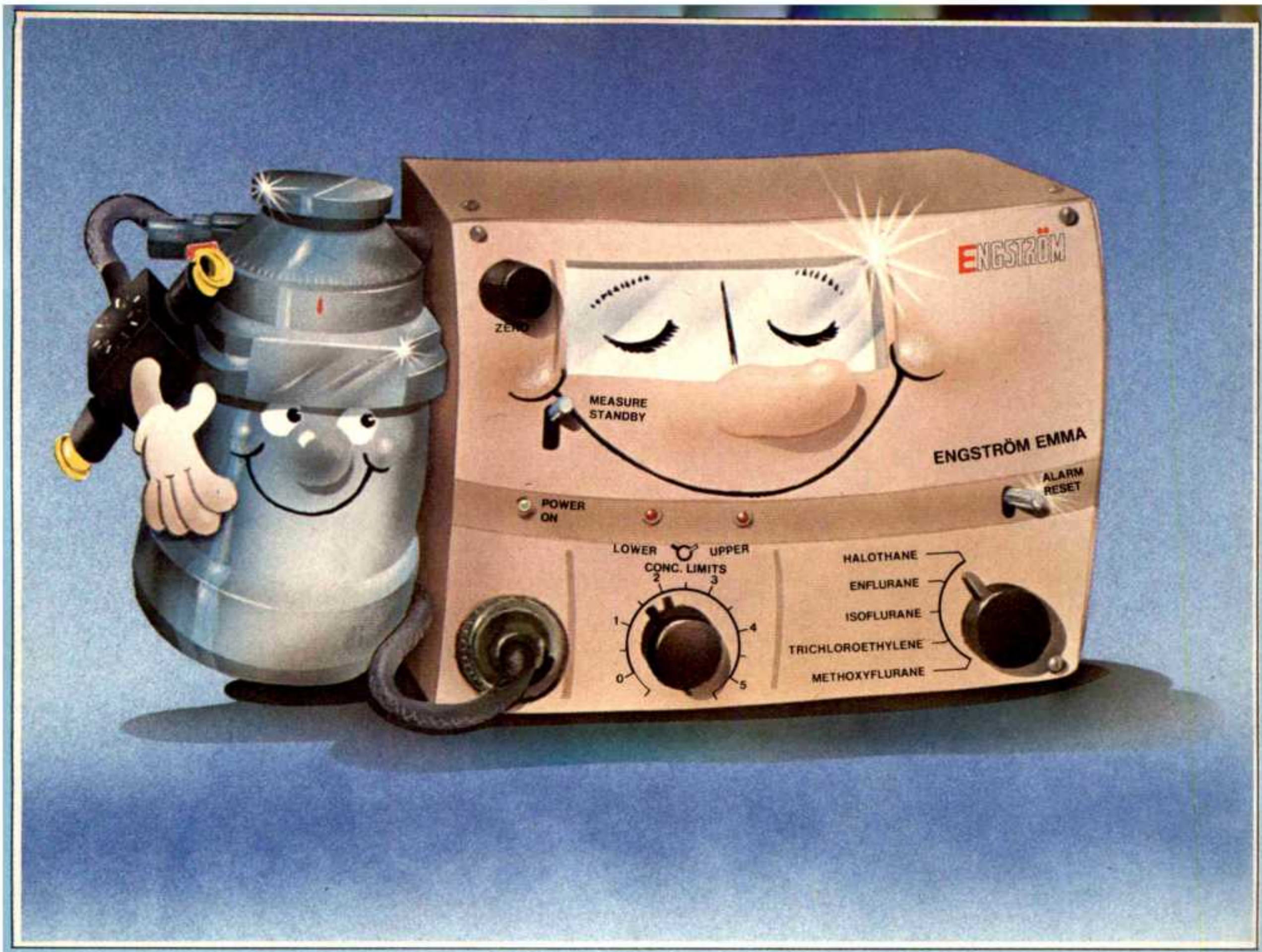
2 TUES
3 WED
4 THUR
5 FRI
6 SAT
7 SUN
Temgesic
i.v./i.m. 1ml
buprenorphine
in 1ml

**Temgesic**
buprenorphine hydrochloride
**Injection**
**For the first few hours**

**Temgesic**
buprenorphine hydrochloride
**Sublingual**
**For the next few days**



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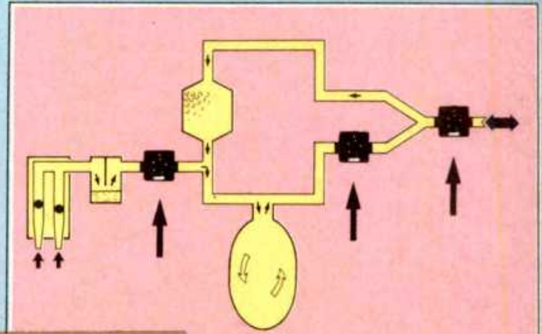
If you have not seen the Engström Emma, ask for a demonstration.



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Lecturer:
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HK$18,225 – 20,685 by 3 increments
(Exchange rate: US$1 = HK$6.6,
£1 = HK$11.2 as at mid-October, 1982)

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*Application Procedure:* Applications should be made out in duplicate, giving full particulars, experience and the names and adresses of 3 persons to whom reference may be made, and sent together with copies of certificates/diplomas/testimonials and recent publications, to the Personnel Section, The Chinese University of Hong Kong, Shatin, N. T., Hong Kong not later than *January 31. 1983.* Please mark "Recruitment" on cover.

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The patient's frontal muscle EMG and electrical activity of the brain (EEG) are recorded with disposable prefilled electrodes. Horizontally compressed displays of frontal EMG and average EEG frequency and amplitude form a comprehensive display for routine anesthesia monitoring.

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Automatic calibration and search for supramaximal stimulus allow easy and fast set-up. The EMG-response to TOF stimulus is updated every 20 s.

**$CO_2$ MONITOR UNIT**

Continuous display and trends with adjustable high and low end-tidal alarm limits.

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Shows the trends of your patient's frontal EMG, average EEG frequency and amplitude, NMT, and respiratory gas $CO_2$.

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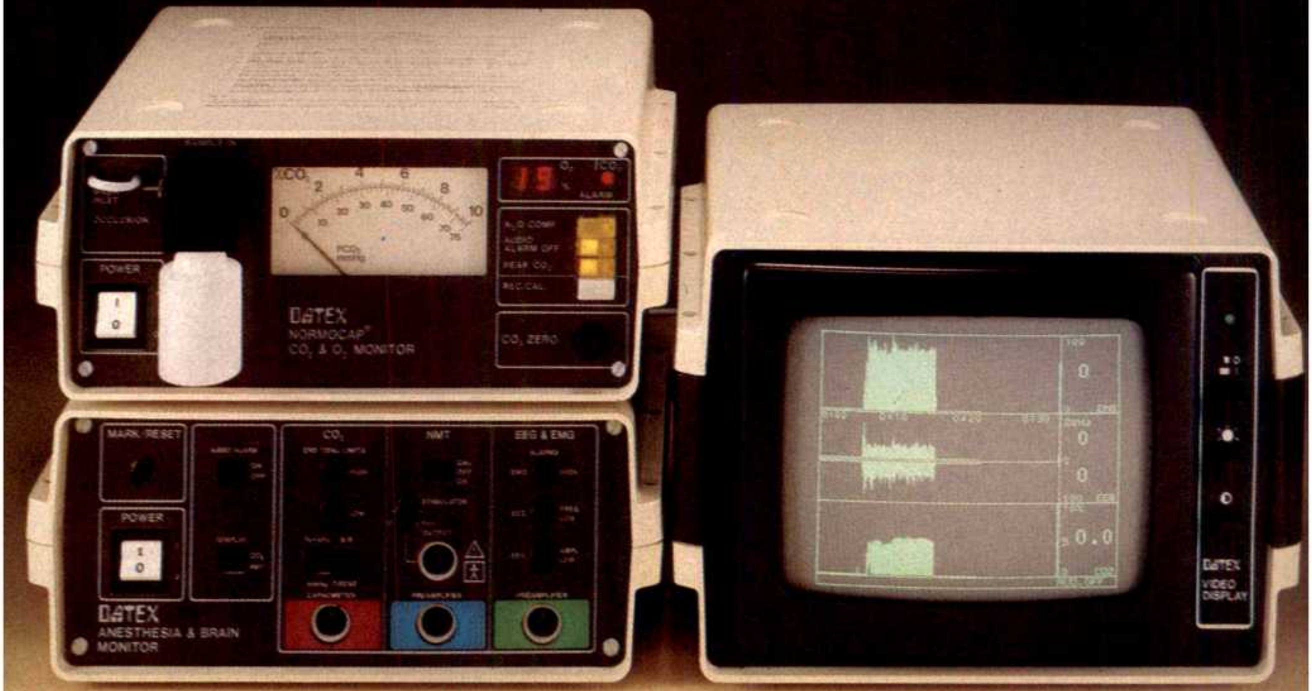

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Telex 124687 instr sf

# 25 years of ‘Fluothane’

Halothane

# in one week?

Anaesthesiology, held at the Royal Festival Hall, London, from 8-15 September, delegates had the opportunity to enter a unique competition presented by ICI Pharmaceuticals Division.

The ‘Fluothane’ 25 Years Competition featured a photographic montage of events of international significance which occurred in each of the twenty five years from the launch of ‘Fluothane’ to the present day. Entrants were required to name the year in which each of the events occurred.

For the benefit of those delegates who were ultimately defeated by the task, and for the interest of other readers of this Journal, the Competition is reproduced here, together with the correct answers.

21.

15.

10.

18.

2.

22.

13.

17.

6.

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3.

4.

he 'Fluothane' 25 Years Competition, r R M Barker, of Northampton General ospital. To the many hundreds of nsuccessful entrants, we should like to xpress our thanks for their efforts and ish them better luck for the 'Fluothane' olden Jubilee Competition!

Imperial Chemical Industries PLC
Pharmaceuticals Division
Alderley Park Macclesfield
Cheshire England

1. 1957 Mayflower II recreates voyage of Pilgrim Fathers
2. 1958 Kruschev becomes Premier of USSR
3. 1959 Fidel Castro takes power in Cuba
4. 1960 Mrs Bandaranaike of Ceylon becomes first woman Prime Minister
5. 1961 Yuri Gagarin makes the first manned space flight
6. 1962 Death of Marilyn Monroe
7. 1963 Assassination of President J F Kennedy
8. 1964 Martin Luther King receives Nobel Peace Prize
9. 1965 Death of Winston Churchill
10. 1966 Florence and its art treasures suffer devastating floods
11. 1967 Francis Chichester completes the first single-handed voyage around the world
12. 1968 Russian tanks enter Prague
13. 1969 First man on the moon
14. 1970 Death of Charles de Gaulle
15. 1971 Idi Amin takes power in Uganc
16. 1972 President Nixon meets Mao Tse Tung in China
17. 1973 Great Britain joins the European Economic Communi
18. 1974 Alexander Solzhenitsyn expell from Russia
19. 1975 Restoration of Spanish Monarc
20. 1976 Concorde goes into service
21. 1977 President Sadat of Egypt mak historic peace mission to Israe
22. 1978 Birth of Louise Brown, the first "test tube" baby
23. 1979 Soviet forces enter Afghanistan
24. 1980 Eruption of Mount St Helens, Washington, USA
25. 1981 Prince Charles and Lady Diana Spencer marry
26. 1982 Argentina occupies the Falkla Islands

2.

9.

8.

26.

19.

11.

20.

# Fluothane
## Still the world's most widely used volatile anaesthetic

**Prescribing Notes**
**Dose:** Induction, 2-4% (adult), 1.5-2% (child); maintenance, 0.5-2% (adult, child); in $O_2$ or $N_2O/O_2$.
**Precautions:** 'Fluothane' anaesthesia should be maintained in the lightest possible plane during obstetric procedures; the use of moderate hyperventilation during neurosurgery is recommended to counteract possible rise in CSF pressure. Adrenaline should be given with caution.
**Side effects:** Malignant hyperpyrexia has been reported in some patients receiving 'Fluothane'.
**Contraindications:** The appearance of jaundice following exposure to 'Fluothane' should be regarded as a contraindication to its later use. Inhalational anaesthesia should be avoided in early pregnancy, unless its use is essential. **P.L.No:** 0029/5058. 'Fluothane' is a trade mark for Halothane Ph. Eur.
Detailed information is available upon request.

# GUIDE TO CONTRIBUTORS

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. Two issues each year deal mainly with material of postgraduate educational value.

## PAPERS

Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the journal and permission to republish must be obtained from the publishers.

Papers based on clinical investigation should conform to ethical standards as set out in the Declaration of Helsinki. In the case of animal studies it is the responsibility of the author to satisfy the Board that no unnecessary suffering has been inflicted.

## LEGAL CONSIDERATIONS

Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the author and publishers.

## PREPARATION OF MANUSCRIPT

Two copies of each manuscript should be submitted and should indicate the title of the paper, the name(s), qualifications and full addresses) of the author(s), and be in double-spaced typing on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss.

Manuscripts should be accompanied by a formal letter of request for publication which should be signed by all of the authors.

Papers in recent issues of the *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

Title page
Summary
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables
Illustrations

### *Title page*

There should be a separate title page, including the name(s), degrees and address(es) of author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript symbols. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spaces should also be suggested.

### *Summary*

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in the form of a single paragraph which gives a succinct account of the problem, the methods, results and conclusions, and normally should be of 50–150 words. It may be used as it stands by abstracting journals.

### *Introduction*

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

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esthesia. **Dosage and Administration** *Dilute each ampoule before use* in at least 50ml Sodium Chloride Infusion Fluid BP or Dextrose Infusion Fluid B.P. Anaesthesia is induced by infusion of a loading dose of 0.1mg/kg/min for the first
minutes, and maintained thereafter by 0.01mg/kg/min until 5 minutes before the end of surgery. For short operations (15-30 minutes) the duration of loading infusion may be reduced to 5 minutes. **Contra-indications** No absolute
tra-indications. Safety in human pregnancy has not been established although studies in animals have not demonstrated teratogenic effects. As with other drugs the risk should be weighed against potential benefit to the patient.
**e-effects** The use of narcotic analgesics as premedication and during surgery will reduce the uncontrolled spontaneous muscle movements shown by some patients after Hypnomidate administration, in some cases such muscle
vements may limit successful maintenance of anaesthesia. Pain can occur after administration into the small veins of the dorsum of the hand. Use of larger veins reduces pain on injection; venous irritation has also been occasionally
orted following Hypnomidate infusions. Other side effects are rare. **Pharmaceutical precautions** Store at room temperature. The concentrate is stable following dilution for up to one week at room temperature. Hartmann's solution is n
ommended for use with Hypnomidate. A pharmaceutical overage of 0.1ml is included in each 1ml ampoule of the concentrate for infusion. **Basic NHS Cost** Packs of 10 ampoules £33.00 (correct at time of printing).
[illegible]

*Methods*

Methods must be described in sufficient detail to allow the experiments to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

*Drugs*

When a drug is first mentioned it should be given the generic or official name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

*Results*

Description of experimental results, while concise, should permit repetition of the experiments by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. Significance should be given as values of probability. The desired positions of tables and figures may be indicated by written instructions enclosed within lines and brackets, for example:

(TABLE III near here)

*Discussion*

The discussion should not merely recapitulate the experimental results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

*Acknowledgements*

Acknowledgements will be printed in small type. They should be brief, and should include reference to sources of support and sources of drugs not freely available commercially.

*References*

There should be a table of references at the conclusion of the paper. These references should be arranged according to the Harvard system and in alphabetical order. In the text, the year of publication must follow the author's name, more than one paper in any year being indicated by a small letter (a, b, c,) after the date. In the references, the order should be author's name, followed by initials; year of publication in parentheses; title of paper to which reference is made; title of publication underlined with a single line (to indicate italics) and abbreviated in accordance with *Cumulative Index Medicus*; volume number in arabic numerals, underlined with a wavy line (to indicate bold face); the number of the first page in arabic numbers; thus Clarke, M., Evans, D. W., and Milstein, B. B. (1971). Long-term pacing with an inductive coupling system. *Br. Heart J.*, **33**, 65.

In the case of books, the reference should be as follows: name of author and initials; year of publication in parentheses; title of book, underlined; number of edition; page number; town of origin, publisher; for example: Hill, D. W. (1971). *Physics Applied to Anaesthesia,* 2nd edn, p. 212. London: Butterworths.

The *British Journal of Anaesthesia* should be referred to as *Br. J. Anaesth.*

In the text up to three authors should be named before the use of "... et al.". If reference is made to several publications during a particular year, written by a larger group of authors who have alternated the order of authorship, as many names must be written as are necessary to distinguish between the publications, before use of "... et al." in conjuction with the year suffixes a, b, c.

Text references to "unpublished observations" or "personal communications" should not be included in the final list of references. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. Papers which have been submitted and accepted for publication should be included in the list, the phrase "(in press)" replacing volume and page number.

It is essential that authors verify the content and details of references which they list, as this responsibility cannot be accepted by either Editors or Publishers.

*Tables*

All tables should be on separate sheets and be capable, with their captions, of interpretation without reference to the text. They should be numbered consecutively with roman numerals. Units in which results are expressed should be given in brackets at the top of each column, and not repeated on each line of the table. Ditto signs are not used.

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Photographs should be unmounted glossy prints, and should be protected adequately for mailing. Surfaces should not be marred with clips, pins or by heavy writing on the back. Drawings, charts and graphs should be in black india ink on white paper. Illustrations should be clearly numbered on the back, preferably in soft pencil, with reference to the text, and using arabic numerals. They should be accompanied on a separate sheet by a suitable legend. Lettering should be professional-looking, uniform, preferably in a common typeface, large enough to read at a reduced size, and in proportion to the illustrated material. Lines in the original must also be thick enough to allow for reduction. Magnifications, especially in photomicrographs, should be indicated by a scale on the photograph itself, in order to remain appropriate after reduction. Symbols which are to appear in the legend should be chosen from the following available types:

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*Headings in the text.* Six possible grades are available:

1. PART I (capitals)
2. RESULTS (small capitals)
3. Blood-gas analysis (l.c. roman)
4. *The action of drugs* (italics, centre)
5. *Lung function studies* (italics, full out)
6. *Volume.* Large volumes. . (italics, indent)

*Symbols and Abbreviations.* In accordance with Editorial adoption of SI Units, abbreviations and symbols should follow the conventions described in the booklet "Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors" (ed. G. Ellis), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London, W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

*Spelling, etc.* British spelling should be used with "z" rather than "s" spelling in, e.g. organize, organization.

## CORRESPONDENCE

It is proposed that a proportion of the Journal be devoted to correspondence each month. Every effort will be made to ensure that correspondence arising from papers in a recent issue is published without delay, and for this reason, relevant correspondence will be given priority over that pertaining to original research. Authors of correspondence concerning original work will receive proofs at the Editor's discretion.

## PROOFS

These should be corrected and returned to the sub-editor *within 48 hours of receipt.* Overseas contributors should return their proofs by airmail.

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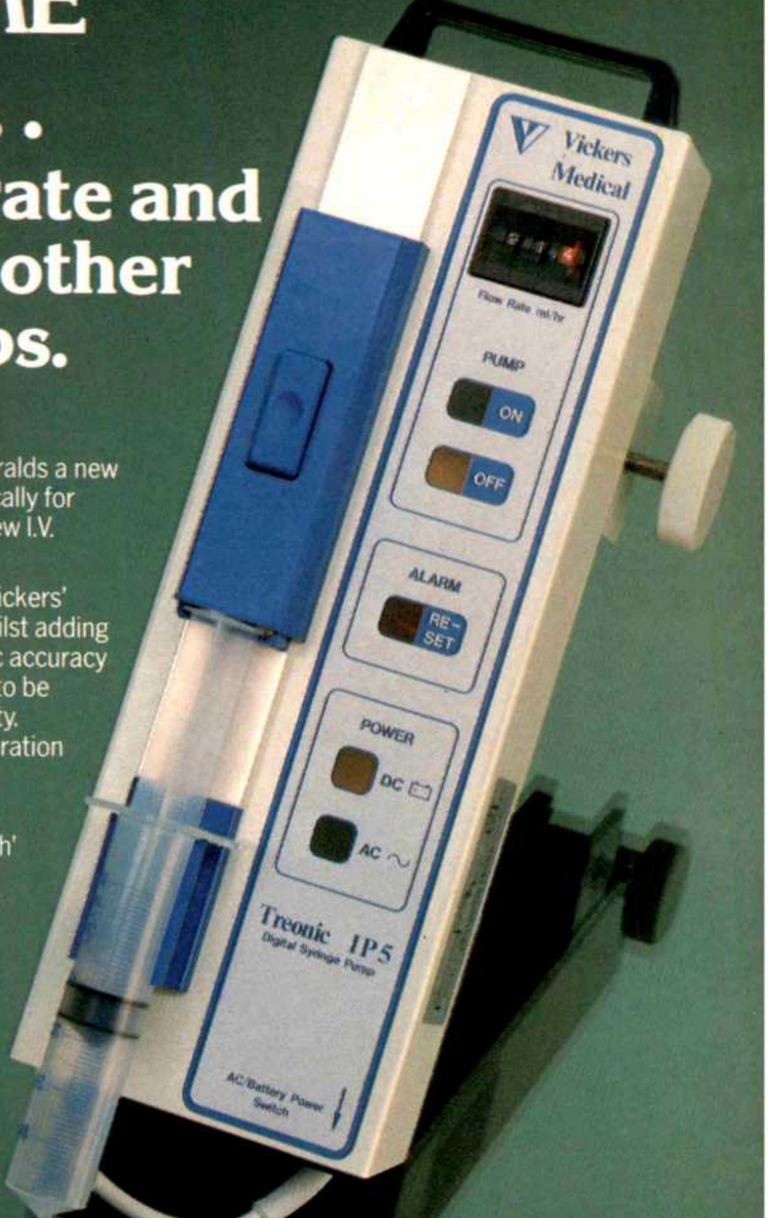
Twenty-five reprints of articles will be dispatched to the authors after publication. Further reprints can be supplied if application is made on the order form attached to the proofs. The order form should be returned with the proofs.



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# Seminars in Anesthesia

Editor
RONALD L. KATZ

Publication: Quarterly
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*Seminars in Anesthesia* will provide the anesthesiologist with a review of important topics in the field. Each issue will be devoted to an area of particular importance in which invited experts will discuss a wealth of clinical experience. All practising anesthesiologists will find *Seminars* a source of current and reliable information.

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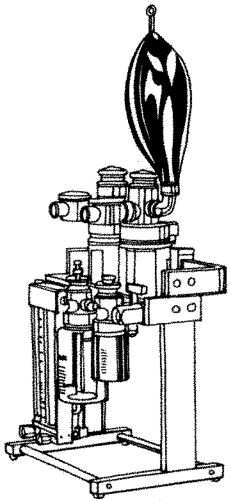

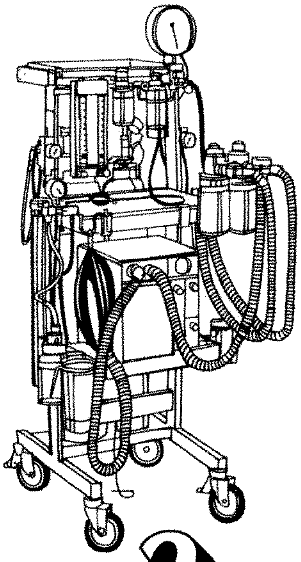

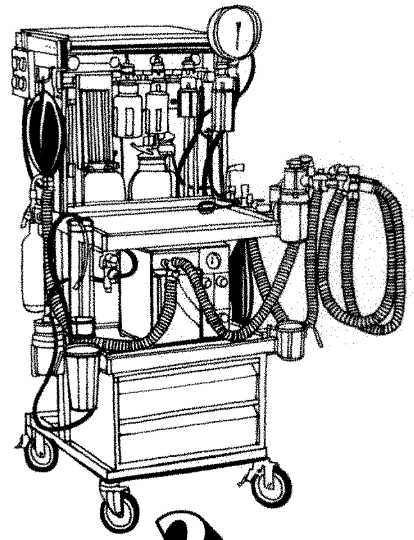

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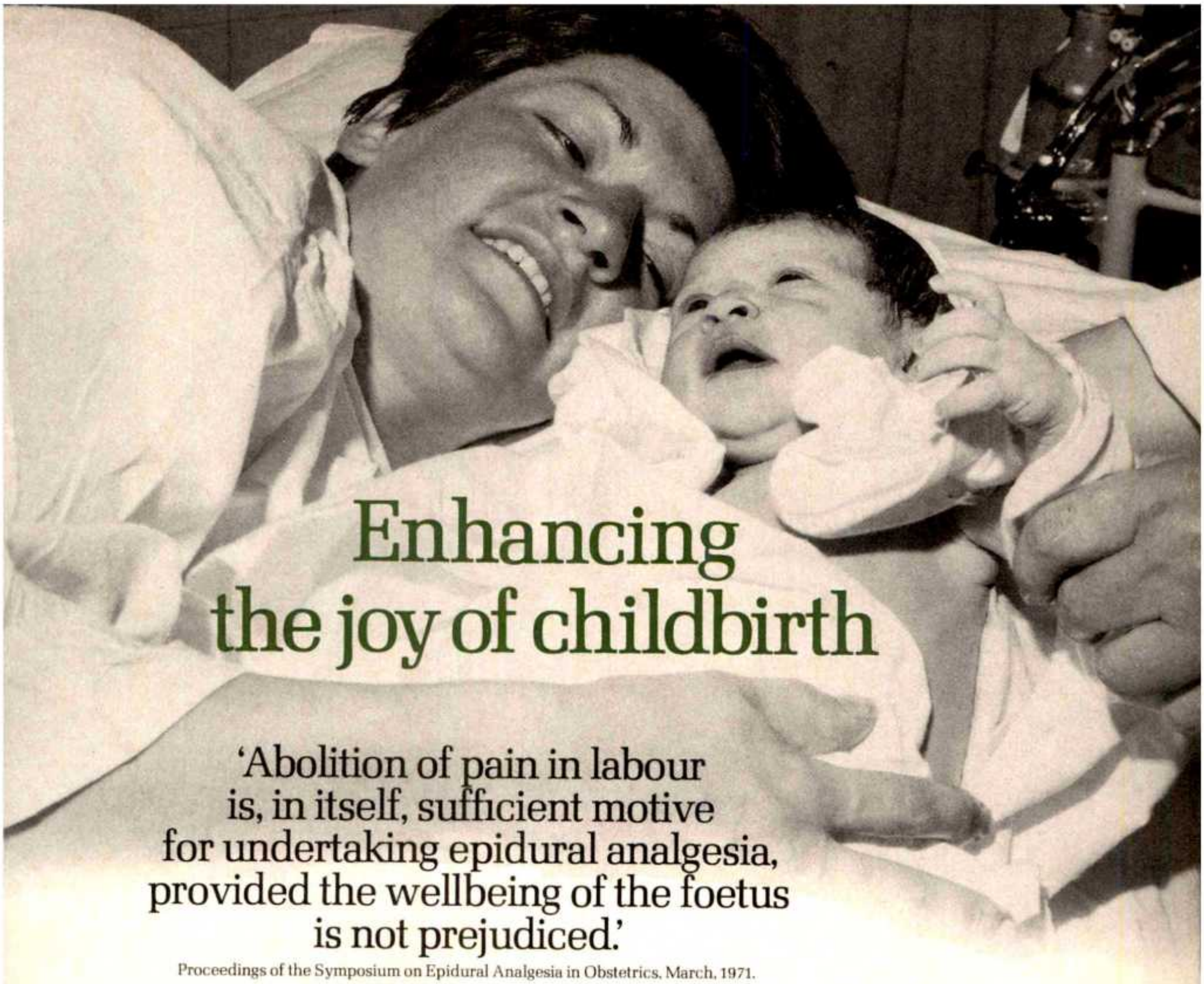

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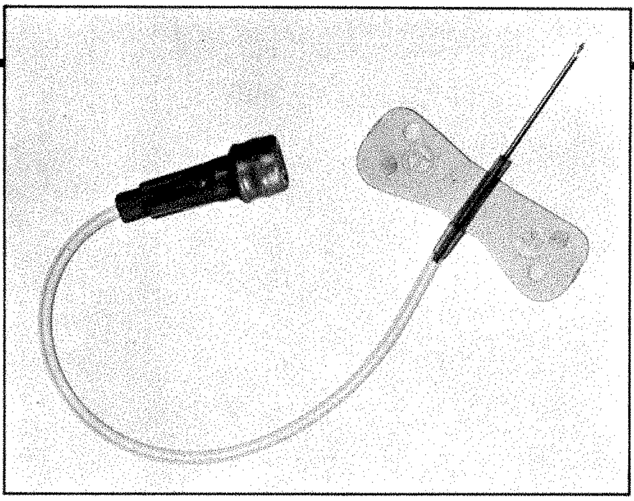

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VOLUME 54, No. 12 DECEMBER 1982

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# USE OF ATRACURIUM DURING GENERAL SURGERY MONITORED BY THE TRAIN-OF-FOUR STIMULI

J. M. HUNTER, R. S. JONES AND J. E. UTTING

## SUMMARY

The use of atracurium in 25 patients undergoing general surgical procedures is described, neuromuscular function being monitored by the "train-of-four" stimuli. An initial dose of atracurium 0.5 mg kg$^{-1}$ proved to be clinically acceptable, giving good conditions for endotracheal intubation and adequate muscle relaxation for about 40 min. Comparison of the results with those from 15 patients given suxamethonium 50 mg showed that atracurium in this dosage took longer to produce complete ablation of the twitch responses but that it lasted longer (about 40 min). Incremental doses of atracurium (of 0.2 mg kg$^{-1}$) gave relaxation for about 30 min and there was no evidence of a cumulative effect. Reversal of the neuromuscular block with neostigmine was prompt and adequate. Using simple clinical means no evidence of an important change in heart rate or arterial pressure was found. There were no adverse reactions to the drug.

Atracurium dibesylate is one of a new series of neuromuscular blocking agents developed by Stenlake (1979). The basic pharmacology of the drug has been described by Hughes and Chapple (1981) and an evaluation of its use in anaesthetized patients has also been published (Payne and Hughes, 1981).

Atracurium is a non-depolarizing agent which breaks down mainly by the so-called Hofmann elimination to give metabolic products which have no neuromuscular blocking effects (Hughes and Chapple, 1981). In addition, *in vivo*, there is some enzymatic hydrolysis, but this does not seem to be an important route of elimination in practice.

Present information indicates that atracurium is stable in solution for at least 18 months at pH 3.5 and temperature 5 °C. However, if the pH be increased to about 7.4 and the temperature to 37 °C, as it is *in vivo*, more than half of an injected dose of the drug is broken down in 30 min.

A non-depolarizing muscle relaxant which breaks down in this way without requiring the kidney or the liver for the termination of its effect might have a conspicuous advantage, especially in such situations as, for example, hypovolaemic shock. It certainly warrants further investigation, especially as it appears to have little or no effect on the cardiovascular system in clinically useful doses.

One of the commonest techniques in present-day anaesthesia is based on the use of a non-depolarizing muscle relaxant with controlled pulmonary ventilation, anaesthesia being maintained with nitrous oxide in oxygen, supplemented with analgesic drugs. At the end of the procedure the residual action of the relaxant is antagonized with neostigmine.

Examination of previous work showed that there was a place for the study of atracurium based on this type of anaesthetic routine. An investigation was undertaken, therefore, the basic technique being modified only to facilitate monitoring of neuromuscular function. In addition, the speed and duration of action of the initial dose of atracurium were compared with those of a dose of suxamethonium 50 mg.

## METHODS

Atracurium was administered to 25 general surgical patients and suxamethonium to 15. In the latter group, who were anaesthetized in precisely the same way as the former, only the results of monitoring neuromuscular function of an initial dose (50 mg regardless of weight) are presented.

Preliminary work with atracurium suggested that an initial dose of 0.5 mg kg$^{-1}$ with incremental doses of 0.2 mg kg$^{-1}$ would be suitable for study. This, it was thought, would give adequate conditions for endotracheal intubation and adequate muscle relaxation for surgical procedures of moderate duration.

### *Patients*

Of the 25 patients receiving atracurium 18 were

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J. M. HUNTER, M.B., F.F.A.R.C.S.: R. S. JONES, DR.VET.MED., F.R.C.V.S.; J. E. UTTING, M.A., F.F.A.R.C.S.; Department of Anaesthesia, University of Liverpool, Royal Liverpool Hospital, P.O. Box 147, Liverpool L69 3BX.

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males. Ages ranged from 21 to 77 yr (mean 48 yr) and weights from 42 kg to 76 kg (mean 61.5 kg). All were physically fit. The operations were intra-abdominal (10) (vagotomy and pyloroplasty, cholecystectomy, etc.), mastectomy or biopsy of breast (eight), hernia (four), partial thyroidectomy (one), varicose veins (one), and haemorrhoidectomy (one). The duration of operation varied from 60 to 324 min (mean 109 min).

Of the 15 patients receiving suxamethonium, seven were males. Ages ranged from 26 to 76 yr (mean 51 yr) and weights from 57 kg to 100 kg (mean 72 kg). All were physically fit. The operations were similar to those in the group receiving atracurium, but are not listed here since the investigations were completed before surgery was commenced.

Informed consent was obtained from all those patients who received atracurium. Approval for the project was obtained from the hospital ethics committee and a clinical trial certificate was obtained.

### *Anaesthesia*

Premedication was with diazepam 10 mg given orally 2 h before operation. Induction of anaesthesia was with fentanyl and droperidol up to 150 μg and 10 mg respectively). This was followed by a small dose of thiopentone (up to 300 mg). Anaesthesia was continued using a mask (with or without an airway), being maintained with a mixture of nitrous oxide in oxygen (5 litre and 2 litre respectively) without any volatile adjuvant, using a Magill attachment. At this stage spontaneous ventilation usually continued, although sometimes assistance was required or ventilation had to be fully controlled, using manual pressure on the reservoir bag.

During this time the equipment for monitoring neuromuscular function was set up. When this had been completed and control measurements taken (in 10–15 min), atracurium 0.5 mg $kg^{-1}$ was administered into a fast running i.v. infusion set up in the arm which was not being used for the monitoring of neuromuscular function. Controlled ventilation (using an anaesthetic mask) was established as soon as practicable and endotracheal intubation was effected, the laryngoscope being inserted 90 s after the drug had been administered. No topical analgesic was applied to the larynx.

The anaesthetist performing endotracheal intubation gave a simple assessment of the conditions for this manoeuvre: thus conditions were to be classified as "good" if the vocal cords were abducted and there was no response (such as cough) in response to the passage of the tube, "adequate" if the only reaction was a slight cough, and "poor" if there was considerable coughing or other movement when the tube was passed. (In those patients who received suxamethonium the procedure was identical except that suxamethonium 50 mg was given instead of atracurium and the investigation was discontinued when the twitch height had returned to 50% of control.)

Controlled ventilation was continued using a mixture of nitrous oxide 70% in oxygen, again without a volatile adjuvant; the patient was taken into the operating theatre and surgery commenced. A circle circuit was used without an absorber, the fresh gas flow and tidal volume being adjusted to give an arterial blood carbon dioxide tension of about 5.3 kPa (Snowdon et al., 1975). To facilitate this an infra-red carbon dioxide analyser (Datex Normocap) calibrated with a mass spectrometer, was used to determine end-tidal carbon dioxide tension.

Increments of fentanyl 25 μg were given if the arterial pressure or heart rate increased during surgery. Increments of atracurium 0.2 mg $kg^{-1}$ were given when indicated by 20% return of the height of the initial twitch response (see below) or, on one occasion, when there was a complaint of poor relaxation.

At the end of surgery atropine 0.6 mg was administered, followed by neostigmine 2.5 mg 1 min later. If the height of the first twitch had not returned to about 75% of control 4 min after the neostigmine was given, atropine 0.6 mg was again administered, followed by neostigmine 2.5 mg after a further 1 min; thus in those patients receiving two doses of neostigmine the time interval between the two was 5 min.

When neuromuscular function had returned to the level which was considered acceptable and there was adequate spontaneous ventilation anaesthesia was discontinued in the usual way and monitoring of neuromuscular function was stopped before the patient became conscious. Consciousness returned rapidly after withdrawal of anaesthesia. When the ability to obey simple commands had returned, the adequacy of muscle power was assessed by asking the patient to lift his head and cough.

Shortly afterwards the patient was sent to the recovery ward and was left there for at least 1 h. The patient was interviewed in the ward the next day and questioned about subjective experiences.

### *Monitoring of cardiovascular function*

Heart rate and arterial systolic pressure (determined by palpation) were recorded at 1-min intervals during induction until the response to train-of-four had disappeared. Later both variables were recorded at intervals of 5 min.

*Blood-gases*

At least two "spot" arterial samples of blood were taken during surgery and blood-gases measured using a blood-gas analyser (Instrumentation Laboratories: IL ABL2C), calibrated in the usual way. A total of 48 samples was taken. These were used to supplement data from end-tidal sampling and confirm that acid–base status was at least near normal limits.

*Monitoring of neuromuscular function*

The train-of-four stimuli was used to monitor neuromuscular function (Ali, Utting and Gray, 1971a,b; Ali and Savarese, 1976). The stimulator was a Grass type S 48. Supramaximal stimuli were applied to the ulnar nerve at the wrist by needle electrodes inserted subcutaneously. The frequency was 2 Hz, the duration of the stimulus 0.3 s (that is there were four stimuli in each train) and the interval between each train was 10 s. The force of thumb adduction was measured using a force-displacement transducer (Grass type, FTO3 C).

It is convenient to designate the heights of the control twitch response to the train-of-four, A, B, C and D before a non-depolarizing muscle relaxant is administered and A′, B′, C′ and D′ thereafter. A, B, C and D are equal, or nearly so, but in states of partial block produced by this type of relaxant "fade" is found, and A′, B′, C′ and D′ each decrease, but in such a way that height A′ > B′ > C′ > D′. If the degree of block is increased D′ disappears first, followed by C′ then B′ and finally A′, recovery taking place in the reverse order. The ratio A′/A and D′/A′ are convenient indications of the degree of block, as is the presence of each individual response; thus if A′ only is present the degree of block is greater than if A′ and B′ are present, and so on.

The initial dose of atracurium completely ablated the response to the stimuli. The time to the first appearance of a degree of block and to the complete disappearance of any mechanical response and the time to recovery of the initial response to 10% of its height before the muscle relaxant was administered (A′/A) was also recorded: at this later stage only two of the mechanical responses of the train-of-four were usually visible. The effect of incremental doses (which again ablated all the twitch responses) was also monitored.

At the end of surgery after neostigmine had been administered monitoring was continued until the initial response of the train-of-four had reached at least 75% of control values (the ratio A′/A was 75%), this being the value at which vital capacity should have returned to normal (Ali et al., 1975); at this time the ratio D′/A′ was also in the order of 70%.

In those patients who received suxamethonium the method of monitoring was identical to that used with atracurium, but it was only the initial dose from which the results of monitoring were recorded.

## RESULTS

*Response of the train-of-four*

The response to the train-of-four stimuli when atracurium was given showed the characteristic "fade" of the non-depolarizing muscle relaxant and eventually all responses disappeared. This is shown in figure 1.

During recovery the initial "twitch" response (A′) re-appeared first, to be followed by B′, C′ and D′, in that order. When an incremental dose was given the twitch responses again disappeared. Figure 2 shows the re-appearance of the responses to the train-of-four and their disappearance when an incremental dose of atracurium had been given.

The mean times (s) to the onset of action of atracurium and suxamethonium and the time to complete disappearance of any response to the train-of-four are shown in table I, as is the mean time (min) to the first reappearance of any response and the time to recovery of the initial response to 10% of its control value. It can be seen that the mean time to disappearance of the train-of-four is shorter with suxamethonium than it is with atracurium; this difference is significant at the usual confidence level ($P < 0.001$; unpaired Student's *t* test). It can also be seen that the mean time to re-appearance is long with atracurium, and this disappearance is again

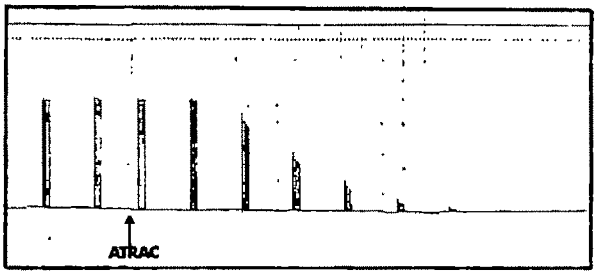

FIG. 1. The disappearance of the responses to the train-of-four stimuli when atracurium 0.5 mg kg$^{-1}$ was administered. The characteristic "fade" can be seen. Each large square represents 5 s.

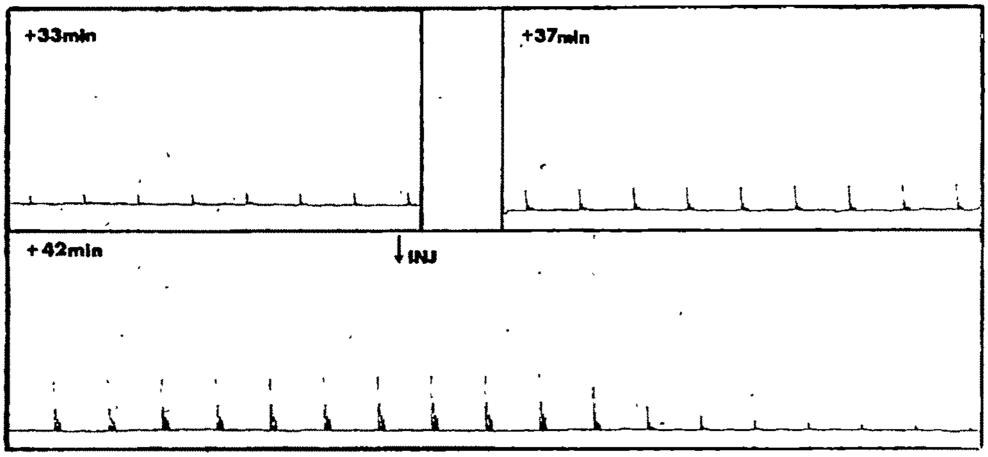

FIG. 2. Stages of recovery of the train-of-four responses. The lower panel shows the effect of an incremental dose of atracurium 0.2 mg kg$^{-1}$.

TABLE I. *Mean times (SD) to first depression of twitch and its disappearance, reappearance and recovery of the initial response to 10% of its control value. The time to the administration of an incremental dose of atracurium is also shown*

| | Atracurium 0.5 mg kg$^{-1}$ | Suxamethonium 50 mg |
|---|---|---|
| No. of patients | 25 | 15 |
| Time to first depression of response (s) | 32<br>(13.6) | 34<br>(10.9) |
| Time to disappearance of response (s) | 110<br>(27.8) | 59<br>(12.1) |
| Time to reappearance of response (min) | 35<br>(7.6) | 6<br>(2.7) |
| Time to 10% recovery of initial twitch height (min) | 39<br>(9.7) | 7<br>(2.8) |
| Time to first increment (min) | 43<br>(11.2) | — |

statistically significant ($P<0.001$; unpaired Student's *t* test). There was no difference between the two relaxants in the time to the first appearance of block.

*Conditions for endotracheal intubation*

The conditions for endotracheal intubation at 90 s, given by the initial dose of atracurium were described as "good" (15 patients: 60%) or "adequate" (10 patients: 40%); none was described as "poor". The investigators were of the opinion that the conditions provided by the initial dose were as good as (or somewhat better than) the conditions provided by the other commonly used non-depolarizing muscle relaxants. In all but one of the patients receiving suxamethonium conditions were described as "good"; the other was described as "adequate".

*Incremental doses*

The mean times from the initial dose of atracurium to each increment are shown in table II. In all but two cases an increment was given when the initial twitch response had reached 20% of its height before the atracurium had been administered. At this time the ratio of the fourth response to the first response was also about 20%.

Incremental doses had to be administered every 10–30 min after the preceding dose had been given. There was no obvious evidence of accumulation with the number of incremental doses used, which ranged up to five (up to a total dose which was three times as large as the dose used for endotracheal intubation).

*Antagonism of neuromuscular block*

Neostigmine effectively antagonized the neuromuscular block (fig. 3). One or two doses of neostigmine (2.5 mg) was given according to the degree of recovery (see methods). An initial dose was given and 4 min later a decision was made as to whether or not a second dose should be given.

In 11 of the patients the ratio of the height of the first twitch response the control (A'/A) was 75% or

TABLE II. *The times (SD) from the administration of the initial dose of atracurium to the incremental doses (0.2 mg kg$^{-1}$). An indication of the degree of block remaining when the increments were administered is given by the ratios A'/A and D'/A'*

| Increment No. | No. receiving | Mean time (min) | Range (min) | Mean A'/A (%) | Mean A'/D' (%) |
|---|---|---|---|---|---|
| 1 | 10 | 43<br>(11) | 21–65 | 19 | 21 |
| 2 | 7 | 71<br>(20) | 35–100 | 23 | 18 |
| 3 | 3 | 89<br>(21) | 50–108 | 19 | 14 |
| 4 | 2 | 99<br>(40) | 63–142 | 22 | 19 |
| 5 | 2 | 129<br>(73) | 78–180.5 | 30 | 23 |

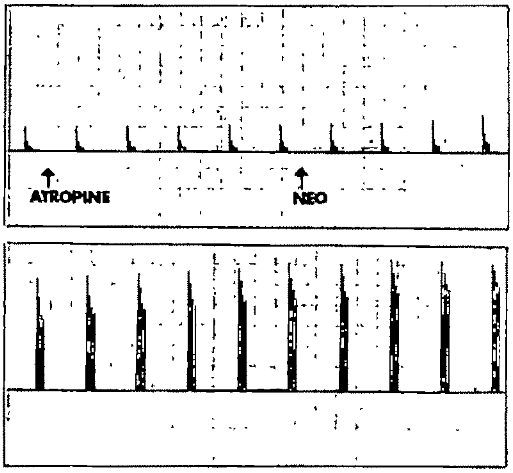

FIG. 3. Reversal of block with neostigmine. The top panel shows the accelerating recovery after neostigmine: after 2 min, recovery is almost complete (lower panel).

more (range 100–75%) at a time of 4 min after a first dose of neostigmine had been given: at the same time the ratio of the fourth twitch height to the first (D'/A') was within the range 100–47%. No further neostigmine was given.

In the other (14) patients the ratio A'/A was less than 75% (72–27%) 4 min after the first dose of neostigmine, the ratio D'/A' at this time being in the range 40–2%. These patients received a further dose of neostigmine 2.5 mg (preceded, as before, by atropine 0.6 mg) 1 min later—that is 5 min after the first dose of neostigmine.

The increase in twitch height with time in the group of patients receiving only one dose of neostigmine is shown in figure 4. It can be seen that the administration of neostigmine is followed by a greatly increasing rate of recovery of both ratio A'/A and D'/A'.

The corresponding results from the group of patients receiving two doses of neostigmine are shown in figure 5. Here the ratios A'/A and D'/A' were lower than in previous group before neostigmine was administered and the rate of recovery at the time was also slower. It can be seen that, although the rate of recovery accelerated greatly after the first dose of neostigmine, it is not possible adequately to assess the effect of the second dose.

### *Blood-gases*

In all 48 "spot" arterial blood samples were taken from the patients. The mean pH was 7.34 (range 7.27–7.48) and mean $Pa\text{CO}_2$ was 5.0 kPa (range 3.6–6.0 kPa). There was thus no evidence of gross alkalaemia (or acidaemia) in the series.

### *Cardiovascular variables*

No clinically significant changes in arterial pressure or heart rate which could be attributed to atracurium were observed after either the initial or incremental doses of the drug. For example, the mean heart rate and systolic pressure just before the atracurium was administered were 76 beat min$^{-1}$ and 127 mm Hg respectively. After the large initial dose had been administered (just before endotracheal intubation was performed) the corresponding figures were 77 beat min$^{-1}$ and 117 mm Hg respectively.

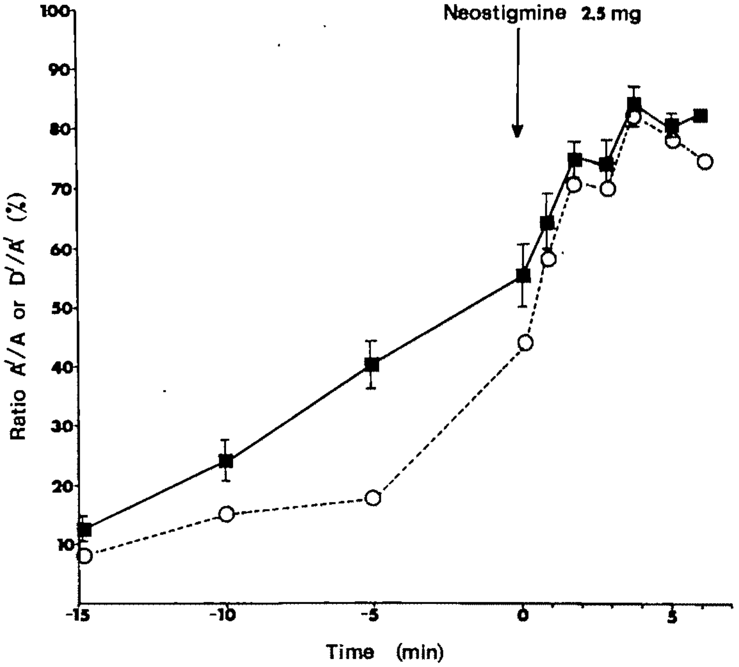

FIG. 4. The effect of neostigmine in those patients to whom only one dose (of 2.5 mg) was administered. The top line (■) shows the mean of the ratio A'/A (as percentage) and SEM. The lower line (○) shows the mean of the ratio D'/A' (as percentage); the SEM is not delineated (to avoid confusion). The increased rate in recovery from block is clearly seen.

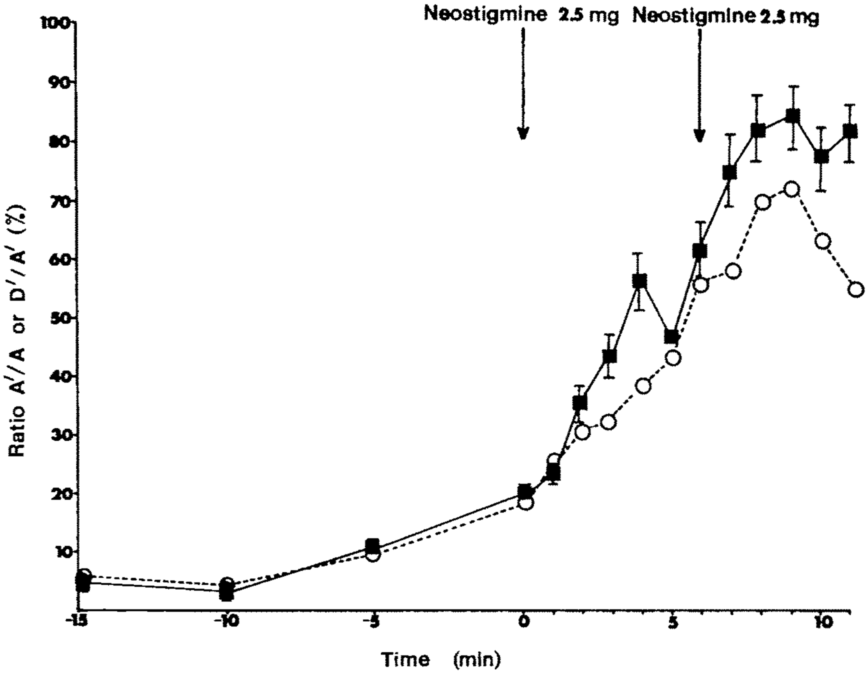

FIG. 5. The effect of neostigmine in those patients to whom two doses (each 2.5 mg) were administered. As in figure 4 the upper line (■) represents A'/A (with SEM) and the lower (○) D'/A'. There is rapid antagonism of neuromuscular block. It is difficult, however, to assess the effect of the second dose of neostigmine.

The investigators sought, but did not find, clinical evidence of histamine release. In three of the patients (all female) a transient flush was seen over the face and shoulders after the administration of the first dose of atracurium, which cleared within 2–3 min. This was not accompanied by any change in arterial pressure.

### *Postoperative interviews*

No subjective accounts suggesting postoperative muscle weakness were obtained. There were no complaints of diplopia, either voluntered spontaneously or elicited by questioning.

## DISCUSSION

Atracurium is not as rapid in action as suxamethonium; this is shown by the fact that the time to complete disappearance of the response to the train-of-four stimuli is longer with atracurium using doses which might be considered as clinically acceptable in both cases. Atracurium will not replace suxamethonium in those circumstances in which speed of tracheal intubation is important. Similarly, the duration of action of suxamethonium is shorter than that of atracurium.

The incremental doses of atracurium used in this study were large in comparison with the dose for endotracheal intubation: thus, for example, if it be conceded that the initial dose of atracurium is equivalent, in terms of conditions provided for endotracheal intubation, with tubocurarine in a dose in the order of 45 mg given to a patient of 70 kg body weight, then the incremental doses of atracurium would be equivalent to about 18 mg of the older drug. Despite this, recovery from each and every incremental dose of atracurium was rapid, even when up to five incremental doses had been administered. There was prompt reversal of the block by neostigmine and no diplopia after operation. However, the ultimate evidence that atracurium is non-cumulative will come from pharmacokinetic studies, although clinical studies of atracurium in renal failure (Hunter, Jones and Utting, 1982—accompanying paper) indicate that atracurium is non-cumulative.

Antagonism of the neuromuscular block with neostigmine was satisfactory. Inspection of the graphical results shows that, in those to whom one dose was administered (fig. 4), there was prompt reversal of the block: this is not surprising since, in this group, the block was wearing off rapidly. In the other group, to whom two doses were administered, antagonsim also appeared satisfactory, although here the degree of block present was greater before the neostigmine was given (fig. 5).

Close inspection of figure 5 reveals that the second dose of neostigmine may, indeed, have been associated with the development of a further degree of "fade". Payne, Hughes and Al Azawi (1980) described such a phenomenon and as it could, in some circumstances, be antagonized with gallamine and potentiated by suxamethonium, they suggested that the neostigmine was producing an acetylcholine-induced block. It may be that the use of neostigmine 5 mg in the current series represented an overdosage relative to the residual block and that one dose of 2.5 mg would have been sufficient.

Cardiovascular monitoring in this series was recognizably crude. Nevertheless, there can be little doubt that there is little gross upset when the drug is used as it was here. There was no observable change in arterial pressure or in heart rate attributable to the drug.

Atracurium thus seemed to be a suitable non-depolarizing muscle relaxant for use in general surgical procedures. If, as pharmacological studies suggest, it is non-cumulative, it proves to be a useful agent both in general use and, more especially, in such situations as renal failure and shock.

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## REFERENCES

Ali, H. H., and Savarese, J. J. (1976). Monitoring of neuromuscular function. *Anesthesiology*, 45, 216.

Utting, J. E., and Gray, T. C. (1971a). Quantitative assessment of residual antidepolarizing block (part I). *Br. J. Anaesth.*, 43, 473.

——— ——— (1971b). Quantitative assessment of residual antidepolarizing block (part II). *Br. J. Anaesth.*, 43, 478.

—— Wilson, R. S., Savarese, J. J., and Kitz, R. T. (1975). The effect of tubocurarine on indirectly elicited train-of-four muscle response and respiratory measurements in humans. *Br. J. Anaesth.*, 47, 570.

Hughes, R., and Chapple, D. J. (1981) The pharmacology of atracurium; a new competitive neuromuscular blocking agent. *Br. J. Anaesth.*, 53, 31.

Payne, J. P., and Hughes, R. (1981). Evaluation of atracurium in anaesthetized man. *Br. J. Anaesth.*, 53, 45.

——— ——— Al Azawi, S. (1980). Neuromuscular blockade by neostigmine in anaesthetized man. *Br. J. Anaesth.*, 52, 69.

Snowdon, S. L., Powell, D. L., Fadl, E. T., and Utting, J. E. (1975). The circle system without absorber used with controlled ventilation. *Anaesthesia.*, **30**, 323.

Stenlake, J. B. (1979). Ions—cyclic nucleotids—cholinergy; in *Advances in Pharmacology and Therapeutics* (ed. J. C. Stoclet), p. 303. Oxford and New York: Pergamon Press.

## UTILISATION DE L'ATRACURIUM EN CHIRURGIE GENERALE, CONTROLEE PAR LE STIMULUS DU TRAIN DE QUATRE

### RESUME

Cet article décrit l'utilisation de l'atracurium chez 25 patients subissant un acte de chirurgie générale, la jonction neuromusculaire étant surveillée par le stimulus du "train de quatre". Une dose initiale de 0,5 mg kg$^{-1}$ s'est révélée cliniquement acceptable, fournissant de bonnes conditions d'intubation endotrachéale et un relâchement musculaire satisfaisant pendant environ 40 min. Si on compare les résultats à ceux de 15 patients ayant reçu 50 mg de suxaméthonium, on voit qu'à cette posologie l'atracurium met plus longtemps à induire une suppression complète des réponses au twitch mais que sa durée d'action est plus longue (environ 40 min). Des doses successives d'atracurium (de 0,2 mg kg$^{-1}$) ont entraîné un relâchement pendant environ 30 min sans qu'il y ait de signe d'effect cumulatif. L'annulation du bloc musculaire par la prostigmine était rapide et complète. L'utilisation de contrôles cliniques simples n'a pas montré de modifications importantes de fréquence cardiaque ou de pression artérielle. Le produit n'a pas entraîné d'effets secondaires néfastes.

## VERWENDUNG VON ATRAKURIUM BEI ALLGEMEINNARKOSE UND ÜBERWACHUNG MIT HILFE VON "TRAIN-OF-FOUR" REIZEN

### ZUSAMMENFASSUNG

Es wird die Verwendung von Atrakurium bei 25 Patienten, die sich einer Operation in Allgemeinnarkose unterziehen mußten, beschrieben, wobei die neuromuskuläre Funktion durch "train-of-four" Reize überwacht wurde. Eine Anfangsdosis von Atrakurium 0,5 mg kg$^{-1}$ erwies sich als klinisch brauchbar, da sie gute Bedingungen für die endotracheale Intubation und adäquate Muskelrelaxierung für ungefähr 40 min ergab. Ein Vergleich der Ergebnisse mit denen von 15 Patienten, die Suxamethonium 50 mg erhalten hatten, zeigte, daß es bei Atrakurium in dieser Dosierung länger dauerte, bis die Zuckungsreaktionen vollständig aufhörten, daß aber die Wirkung länger andauerte (ungefähr 40 min). Zusätzliche Dosen von Atrakurium (0,2 mg kg$^{-1}$) ergaben eine Relaxierung für ungefähr 30 min ohne Anzeichen für eine Akkumulation. Die Antagonisierung mit Neostigmin erfolgte schnell und adäquat. Bei Benutzung der einfachen klinischen Mittel waren keine Anzeichen für eine wichtige Veränderung der Herzfrequenz oder des arteriellen Blutdruckes zu finden. Es traten keine unerwünschten Wirkungen auf.

## USO DEL ATRACURIO DURANTE CIRUJÍA GENERAL CONTROLADA POR LOS ESTIMULOS EN SERIE DE CUATRO

### SUMARIO

Se da una descripción del uso del atracurio en 25 pacientes sometidos a operaciones quirúrgicas generales, la función neuromuscular encontrándose controlada por los estímulos en serie de cuatro. Se comprobó que una dosis inicial de atracurio de 0,5 mg kg$^{-1}$ era clínicamente aceptable y que daba buenas condiciones para la intubación endotraqueal así como un relajamiento muscular adecuado durante 40 min aproximadamente. Al comparar los resultados con los obtenidos en 15 pacientes a los cuales se administró 50 mg de suxametonio, se demostró que el atracurio en esa dosis exigía un periodo mayor para producir una ablación total de las respuestas de contracción, pero que su efecto duraba más tiempo (alrededor de 40 min). Dosis crecientes de atracurio (de 0,2 mg kg$^{-1}$) produjeron un relajamiento de cerca de 30 min y no hubo prueba de un efecto cumulativo. La inversión del bloqueo neuromuscular con neoestigmina fue rápido y adecuado. Al usar medios clínicos simples, no se halló ningun a prueba de cambio importante del ritmo cárdiaco o de la presión arterial. No hubo reacciones adversas a dicha substancia.

*Br. J. Anaesth.* (1982), 54, 1251

# USE OF ATRACURIUM IN PATIENTS WITH NO RENAL FUNCTION

J. M. HUNTER, R. S. JONES AND J. E. UTTING

## SUMMARY

Atracurium was given to 26 patients who had no renal function; in 21 of these neuromuscular block was monitored using the train-of-four stimuli. The results are compared with those obtained from normal patients presented for surgery. Unlike the non-depolarizing muscle relaxants currently in common use, it was possible to continue giving incremental doses of atracurium to the anephric patients without there being evidence of cumulation. Even when the total dose used (over a period of up to 2.5 h) was in the order of seven to eight times that previously described as the minimum required for endotracheal intubation (2.3 mg kg$^{-1}$ as opposed to 0.3 mg kg$^{-1}$), there was no evidence of residual curarization. This finding would seem to be compatible with what is known of the pharmacology of the drug. No adverse cardiovascular effects were demonstrated. It is concluded that atracurium may be especially valuable in patients with no renal function.

Atracurium dibesylate is a new non-depolarizing muscle relaxant. Its pharmacology has been described by Hughes and Chapple (1981), and its clinical use by Payne and Hughes (1981).

Atracurium is stable in solution for at least 18 months at pH 3.5 and temperature 5 °C and in an ampoule it retains 90% of its potency for 1 month when kept at a room temperature of 27 °C. If, however, the pH is increased to about 7.4 and the temperature to 37 °C (as *in vivo*) it breaks down, mainly by the so-called Hofmann route, and in these circumstances the half-life of a dose of the drug is less than 30 min. Renal excretion is not an important method of elimination.

The non-depolarizing muscle relaxants in common clinical use are all eliminated to some degree by the kidney and it is usually suggested that it is for this reason that their use in patients with renal failure is associated with the risk of persistent curarization, or even of recurarization. As atracurium is not eliminated by the kidney it would seem to have advantages in renal failure. Unfortunately, the measurement of atracurium in plasma is very difficult, especially so since the molecule breaks down.

A clinical study was undertaken of the use of the drug in anephric patients. A total of 26 patients was studied; in 21 of these the neuromuscular block was assessed using the train-of-four stimuli and in the other five assessment was purely on clinical impression. The results obtained were compared with those from 25 surgical patients who had normal renal function, as reported in an accompanying paper (Hunter, Jones and Utting, 1982b). A preliminary communication on some aspects of atracurium in renal failure has already appeared (Hunter, Jones and Utting, 1982a).

## METHODS

### *Patients*

Twenty-six patients were studied. None had any renal function and all were being treated before operation with regular haemodialysis. Most (16) were being treated with one or more antihypertensive agents; these were labetalol (seven patients), metoprolol (six), hydrallazine (three), propranolol (two), clonidine (one) and tranxene (one). In addition most were receiving preparations of iron, vitamins and antacids.

Of the 26 patients 19 were males; the average age was 40 yr (range 21–61 yr) and weight 61 kg (range 40–84 kg). The mean haemoglobin concentration was 8 g dl$^{-1}$ (range 4.6–15.8 g dl$^{-1}$).

Plasma electrolyte concentrations were within normal limits, except that there was a mild degree of metabolic acidosis usual in patients with chronic renal failure (mean = −7.3). Creatinine concentrations were between 358 and 1368 mmol litre$^{-1}$ (mean 897 mmol litre$^{-1}$) and urea between 6 and 48 mmol litre$^{-1}$ (mean 21.3 mmol litre$^{-1}$). The general condition of the patients was as good as might be expected for patients of this type.

Surgery was performed for graft nephrectomy

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(eight patients), for renal transplant (seven) and for the establishment (or revision) of an arterio–venous fistula (four). The other operations, each involving one patient, were exploration of graft, transurethral resection of prostate, vagotomy and pyloroplasty, insertion of peritoneal dialysis cannula, exploration of iliac artery, laparotomy and nephro–ureterectomy.

The trial had the approval of the hospital ethical committee. Informed consent was obtained from each patient.

### *Anaesthesia*

This was described in detail in the preceding paper (Hunter, Jones and Utting, 1982b).

Premedication was with diazepam 10 mg given orally 2 h before surgery. Induction of anaesthesia was with fentanyl and droperidol (up to 150 μg and 5 mg respectively). This was followed by a small dose of thiopentone (up to 300 mg). In those patients in whom monitoring of neuromuscular function was carried out (21) anaesthesia was continued with nitrous oxide in oxygen using a face-mask until the monitoring equipment was set up, pulmonary ventilation being assisted or controlled. No volatile adjuvant was used at any stage of the investigation. Atracurium 0.5 mg $kg^{-1}$ was then given and endotracheal intubation commenced 90 s thereafter. In those patients (five) in whom neuromuscular function was not monitored, atracurium 0.5 mg $kg^{-1}$ was given immediately after induction and endotracheal intubation effected after an interval of 90 s. Conditions for endotracheal intubation were categorized as "good", "adequate" or "poor", as described previously.

Anaesthesia was maintained with a non-hypoxic mixture of nitrous oxide in oxygen, supplemented with fentanyl. Increments of atracurium (0.2 mg $kg^{-1}$) were given in those patients in whom neuromuscular function was monitored when the initial twitch height (designated A′, see below) had reached 10% (or slightly less) of its control value. In two patients, however, a final increment was given when the ratio was higher (about 30%) because it had originally been thought that no further increment would be required. In those patients in whom neuromuscular function was not monitored the increments of atracurium were given when muscular relaxation was deemed clinically to have become inadequate.

At the end of anaesthesia neostigmine 2.5 mg (preceded by atropine 0.6 mg) was given to antagonize the neuromuscular block. If, 4 min after this dose of neostigmine had been administered, the height of the initial twitch response (A′) had not returned to 75% of control (A) atropine 0.6 mg was given immediately, followed 1 min later by a second dose of neostigmine 2.5 mg. Thus the second dose of neostigmine was given exactly 5 min after the first. Anaesthesia was discontinued soon after, but neuromuscular monitoring was continued until just before the patient regained consciousness.

### *Monitoring*

Neuromuscular function was monitored using the train-of-four stimuli (Ali, Utting and Gray, 1971). The precise method has already been described (Hunter, Jones and Utting, 1982b). The twitch heights are conveniently designated A, B, C, and D. Before a muscle relaxant is given, all these heights are equal, or nearly so. In partial block with a non-depolarizing muscle relaxant "fade" occurs. Designating the heights of the twitches as A′, B′, C′, and D′, it can be said that $A' > B' > C' > D'$. If the degree of block increases, D′ disappears first, followed by C′ and so on; on recovery reappearance takes place in the opposite order. The ratios A′/A and D′/A′ are convenient indications of the degree of block: in this paper they are expressed as percentages throughout.

Monitoring of heart rate, arterial pressure and blood-gas tensions has again been described previously.

## RESULTS

When relevant, the results from the 21 anephric patients in whom the train-of-four was used to monitor neuromuscular function are compared with the results obtained, using a similar technique, in 25 normal surgical patients (Hunter, Jones and Utting, 1982b).

### *Response to the train-of-four stimuli*

As in the normal surgical patients, the response to atracurium showed the characteristics of a non-depolarizing block. Thus there was "fade" of the response as paralysis developed and when the response returned it was the first twitch response which reappeared first, to be followed by the second, third and eventually the fourth, in that order. This fade, however, was much more evident on recovery from block than it was during curarization. Additional evidence was provided by the fact that neostigmine effectively antagonized the block (see below).

### *Rapidity of onset and duration of action of initial dose*

The mean time (s) to the onset of paralysis (the time at which some depression of response occurred) and the time at which the response disappeared completely are shown in table I. It can be seen that the initial effect of the atracurium appeared a few seconds later in the anephric patients and that the time to complete ablation of the twitch response was also slower. The difference between the two is significant in both at the usual level of confidence ($P < 0.01$; unpaired $t$ test).

However, the time to the re-appearance of a response to stimulation was slightly shorter in the anephric patient than in the normal patients, although the difference does not reach statistical significance. There is thus no evidence from this series that the initial dose of atracurium was of greater duration in the anephric patients than it was in the normal group.

TABLE I. *Mean times (SD) to first depression of twitch and its disappearance, re-appearance and recovery of initial response to 10% of control value, together with the time of the first increment in both 25 normal and 21 anephric patients*

| | Normal | Anephric |
|---|---|---|
| No. of patients | 25 | 21 |
| Time to first depression of response (s) | 32<br>(13.6) | 53<br>(8.1) |
| Time to disappearance of response (s) | 110<br>(27.8) | 190<br>(58.8) |
| Time to reappearance of response (min) | 35<br>(7.6) | 29<br>(9.6) |
| Time to 10% recovery of initial twitch height (min) | 39<br>(9.7) | 35<br>(11.2) |
| Time to first increment (min) | 43<br>(11.2) | 32.5<br>(11.4) |

### *Conditions for endotracheal intubation*

The conditions provided for endotracheal intubation, performed after 90 s, are shown in table II, again compared with the group of normal patients. Conditions for endotracheal intubation in the anephric patients were acceptable in every case. There were, however, fewer patients in whom conditions were described as "good" in the anephric patients and a greater proportion in whom conditions were described as "adequate". This difference is significant at the usual level of confidence ($P < 0.01$; unpaired $t$ test).

The greater proportion of patients who coughed at intubation must be considered in the light of longer time taken in this group before complete ablation of twitch response occurred. Reference to table I shows that the degree of peripheral block present when endotracheal intubation was effected must have been greater in the normal than in the anephric patients.

### *Effect of incremental doses*

The mean times (min) from the initial dose of atracurium to the incremental doses is shown in figure 1 for both normal and anephric patients and the data on which this is based (for anephric patients only) are shown in table III. It must be noted that, in the normal patients, increments were given when $A'/A$ was about 20%, but in those anephric patients in whom the train-of-four was monitored when $A'/A$ was about 10% (that is at an earlier stage of recovery, since it is clearly desirable in a renal transplant to minimize the possibility of movement during vascular anastomoses).

There was no difference in the mean times at which increments were given up to the fifth incremental dose—after which direct comparison becomes impossible since none of the normal group received more than five incremental doses. Up to nine incremental doses, however, were given to patients in the anephric group, corresponding to a total dose of atracurium of 2.3 mg kg$^{-1}$ body weight.

### *Reversal of neuromuscular block*

Of the 21 patients monitored with the train-of-four 16 were given neostigmine 2.5 mg and five were given 5.0 mg (in two equal doses separated by 5 min as already described). The effect of neostigmine on

TABLE II. *Conditions for endotracheal intubation 90 s after atracurium 0.5 mg kg$^{-1}$ in normal and anephric patients. Conditions were said to be "good" if the cords were abducted and there was no cough on intubation and "adequate" if there was slight cough only on intubation*

| | Normal | Anephric |
|---|---|---|
| No. | 25 | 26 |
| Good | 15<br>(60%) | 9<br>(35%) |
| Adequate | 10<br>(40%) | 17<br>(65%) |
| Poor | 0 | 0 |

TABLE III. *Data on the incremental doses given to the anephric patients. The second column gives the number of patients receiving each increment and underneath (T) is given the number of those on whom train-of-four data were available. The mean time at which each increment was given is shown (SD), as is the range of times. The last two columns give the available data on the state of recovery (as shown by the train-of-four) when each increment was administered*

| Increment no. | No. receiving increment | Mean time (min) | Range (min) | Mean A′/A (%) | Mean D′/A′ (%) |
|---|---|---|---|---|---|
| 1 | 25<br>(T = 18) | 32.5<br>(11) | 11–63 | 9 | 12 |
| 2 | 22<br>(T = 15) | 60<br>(18) | 31–113 | 11 | 8 |
| 3 | 18<br>(T = 13) | 87<br>(28) | 56–175 | 12 | 9 |
| 4 | 9<br>(T = 9) | 99<br>(17) | 61–121 | 10 | 10 |
| 5 | 9<br>(T = 7) | 122<br>(19.5) | 90–145 | 9 | 13 |
| 6 | 7<br>(T = 6) | 152<br>(22) | 122–179 | 13 | 11 |
| 7 | 5<br>(T = 4) | 183<br>(22) | 159–209 | 13.4 | 15 |
| 8 | 2<br>(T = 2) | 216.5<br>(39) | 189–244 | 7.5 | 5.6 |
| 9 | 1<br>(T = 1) | 269 | — | 8 | 12 |

neuromuscular block is shown in figures 2 and 3.

It can be seen that in both cases there was prompt recovery from neuromuscular block as shown by an increase in the ratios A′/A and D′/A′ in both cases. Figure 2 shows that the degree of recovery was some 80% 5 min after the one dose of neostigmine had been given and there was about the same recovery 5 min after the second dose had been given in those who received two doses.

At the end of anaesthesia, after recovery of consciousness, all the patients were able to sustain head-raising off the pillow. There were no complaints of postoperative diplopia the day after surgery.

### *Blood-gas analysis*

"Spot" values for blood-gas analysis (48) showed a mean pH of 7.33 (range 7.21–7.50) and mean $Pa_{CO_2}$ of 4.9 kPa (range 3.4–6.2 kPa). There was no evidence of alkalaemia; in only two of the 48 samples taken during surgery was the arterial pH greater than 7.40. There was (as would be expected in this group) an appreciable degree of metabolic acidosis.

### *Cardiovascular variables*

There was no significant change in heart rate or arterial pressure which could be specifically attributed to atracurium. When the initial dose of atracurium was administered there was a mean decrease of systolic arterial pressure of 17 mm Hg (range −60 to +120 mm Hg) 1 min after the drug had been given. No decrease could be detected when incremental doses were administered. The heart rate appears to be unaffected by the initial dose (although it sometimes increased slightly when endotracheal intubation was performed); during surgery it was usually in the range 70–90 beat min$^{-1}$. There were no, again, discernible changes when incremental doses were given.

## DISCUSSION

The use of the non-depolarizing muscle relaxants in common use in patients with little or no renal function is attended by the risk of prolonged action or even re-curarization. Prolonged muscular paralysis after the use of a non-depolarizing relaxant was first reported in a patient who had poor renal function by Fairley (1950). That agent was gallamine and, over the years, other reports of a prolonged effect of this relaxant in renal failure accumulated (Feldman and Levi, 1963; Singer, Dutton and Way, 1971).

It was initially thought that there should be a normal response to tubocurarine in the absence of renal function, but Riordan and Gilbertson (1971) reported prolonged paralysis in a patient after this agent had been used and, since then, a number of

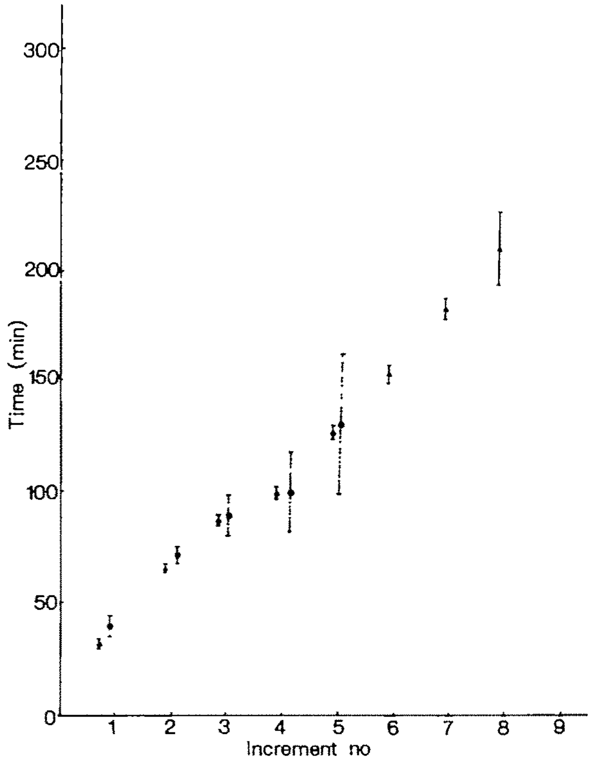

FIG. 1. The mean times (min) for the initial and subsequent incremental doses of atracurium both in the anephric patients (▲) with the standard error (continuous vertical bar) and in those patients with normal renal function (●) together with the standard error (dotted vertical bar).

further reports have appeared either by themselves (for example, Miller and Cullen, 1976) or in the systematic surveys of anaesthesia for renal transplantation mentioned later.

Nor is the use of pancuronium free from these difficulties. Thus Abrams and Hornbein (1975) reported a case in which it proved impossible to reverse the action of this drug with anticholinesterase in a patient with both renal failure and hepatic disease and Geha, Blitt and Moon (1976) presented a further case of prolonged action after the use of pancuronium in renal failure. Studies in patients with renal failure (Miller, Stevens and Way, 1973; d'Hollander, Camu and Sanders, 1978) have confirmed that a prolonged action might be expected with this agent, as have the surveys of anaesthesia for renal transplantation already alluded to.

Although little has been written about the use of alcuronium in renal failure, Havill and colleagues (1978) suggested that its use in such patients "is probably contra-indicated", although they presented little evidence for this, and the conclusion was challenged by other workers (Berry and Benson, 1979). That there is no reason to suppose, from its pharmacokinetic properties, that alcuronium would be conspicuously safer than the three other drugs is suggested by the work of Buzello and Agoston (1978).

These last named workers came to the conclusion, from a computer-based pharmacokinetic study of the known experimental data, that the differences between the muscle relaxants already mentioned is one of degree; there is no fundamental difference in regard to their behaviour in patients with no renal function. In this respect it is interesting to note that even gallamine, which has undoubtedly the worst reputation, has been used successfully in anaesthesia for renal transplant (White, De Weerd and Dawson, 1971). The fact is that all these drugs are cumulative, especially when the renal route of elimination is not present. The skilful anaesthetist usually avoids difficulty by giving much smaller doses of the drugs than to normal patients and, in general, by avoiding incremental doses.

However, reports of persistent curarization, or of recurarization, when gallamine, tubocurarine, pancuronium or alcuronium are used in renal failure give no indication of the size of the problem. The early accounts of anaesthesia for renal transplantation based on retrospective series of patients (Strunin, 1966; Wyant, 1967) mention the danger of persistent neuromuscular block with the non-depolarizing muscle relaxants and Strunin records a case occurring with tubocurarine (one patient in 13 receiving the drug). Logan, Howie and Crawford (1974) found persistent block in 7% of a small series (56 operations) and in two patients (one given pancuronium alone, the other pancuronium with tubocurarine) admission to a respiratory unit was required.

Morgan and Lumley (1975) found that only 1% of patients who received non-depolarizing muscle relaxants (tubocurarine and pancuronium) failed to breathe adequately. On the other hand, Rouse, Galley and Bevan (1977) conducted a retrospective survey of 247 patients requiring renal transplantation, or operations associated with it. Of these seven required controlled ventilation (for up to 6 days) because of persistent curarization or of recurarization; all the cases received tubocurarine or pancuronium. Only 65 patients in this series received

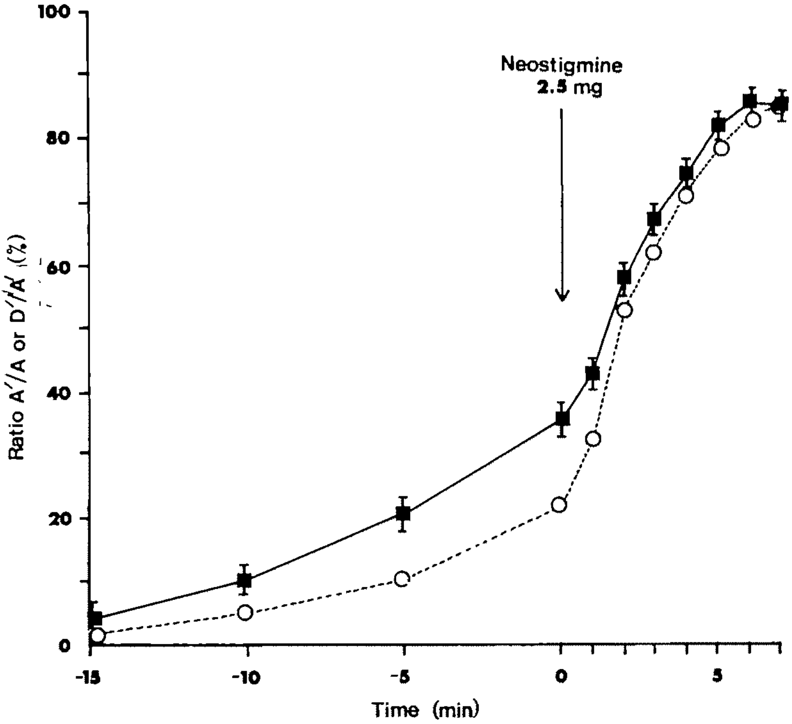

FIG. 2. The effect of neostigmine in those (16) anephric patients to whom only one dose (of 2.5 mg) was administered. The top line (■) shows the means of the ratio A'/A (as percentage) and the SEM. The lower line (○) shows the mean of the ratio D'/A' (as percentage); here SEM is not delineated (to avoid confusion). The increase in recovery from block is clearly seen.

non-depolarizing muscle relaxants and the frequency of side-effects (11%) must be regarded as high. Moreover, difficulty was encountered with a dose of tubocurarine as low as 15 mg and of pancuronium as low as 4 mg.

Fahey and colleagues (1981) suggested that vecuronium (Org NC 45: Norcuron) "may be a suitable non-depolarising muscle relaxant for patients with impaired renal function." This claim was based on a study of pharmacokinetics with monitoring of the twitch response, in 15 patients, of whom four had renal failure. A single small dose (0.15 mg kg$^{-1}$) was given to each of the patients in renal failure over a 2-min period.

As with atracurium there are *a priori* grounds for believing that vecuronium may be a better non-depolarizing agent than the others, since the kidney is not a major route of elimination of the drug. It must, however, be emphasized that it is not by any means proved that, in renal failure, absence of urinary secretion is the only factor causing prolonged curarization. Uraemia is a complex biochemical derangement and other factors may be involved as well.

The results recorded here are compatible with work on the degradation of atracurium recorded elsewhere (Hughes and Chapple, 1981) and suggest that atracurium is a very suitable muscle relaxant for use in patients who have no renal function. The initial dose used in this study (0.5 mg kg$^{-1}$) was considerably larger than the minimum dose required for endotracheal intubation (0.3 mg kg$^{-1}$) and incremental doses (0.2 mg kg$^{-1}$) were large in relation to the initial dose. Assuming that atracurium 0.5 mg kg$^{-1}$ is equivalent, in terms of conditions provided for endotracheal intubation, to tubocurarine 0.65 mg kg$^{-1}$ (that is, equivalent to a dose of 45 mg given to a patient of weight 70 kg), the largest total dose given in this series would be equivalent to something in the order of tubocurarine 200 mg administered to a patient of that weight. Such a dose of tubocurarine in a patient with no renal function would certainly give rise to prolonged paralysis.

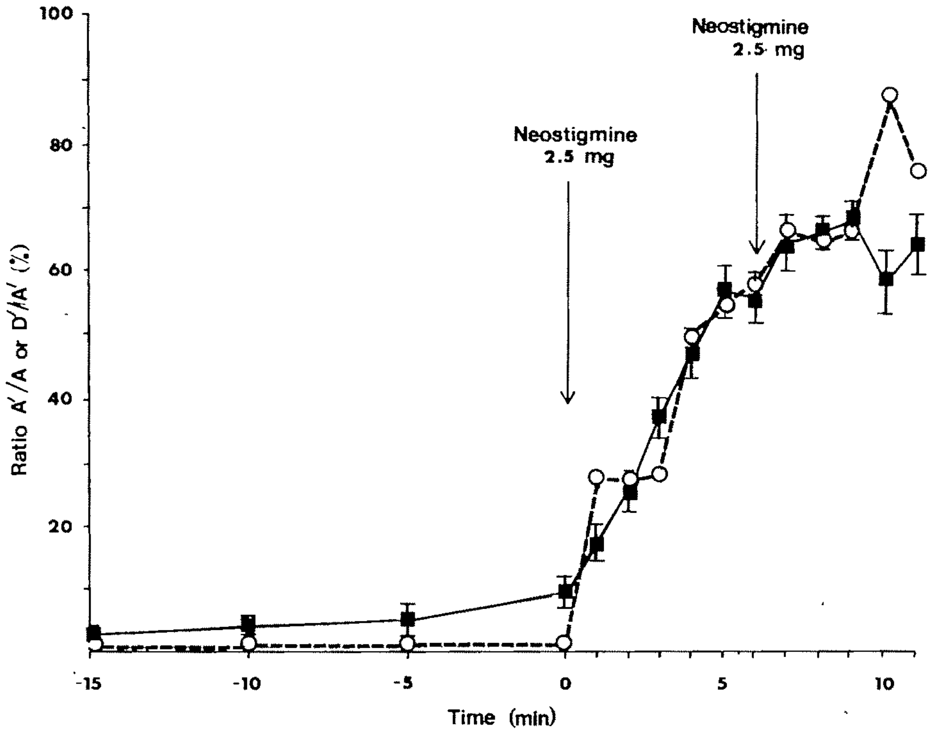

FIG. 3. The effect of neostigmine in those (five) anephric patients to whom two doses (each 2.5 mg) were administered. As in figure 2, the upper line (■) represents A'/A (with a standard error) and the lower (○) D'/A'. There is rapid antagonism of neuromuscular block.

It is argued (and almost certainly correct) that smaller doses of neostigmine should have been used in this study. Certainly, the use of neostigmine 5 mg may have been excessive. Indeed, it is difficult to be sure, from the results, that its use in this high dose may not have been counter-productive.

Although, as has been stated, skilful anaesthetists can usually produce adequate clinical results using the currently available non-depolarizing muscle relaxants, the advent of a drug with a much greater margin of safety in respect of the possibility of persistent curarization would appear to represent a considerable advance in this field.

## ACKNOWLEDGEMENTS

More than merely routine thanks are due to Mr Robert Sells, Mr Donald Scobie and Miss Christine Evans both for helping and actively encouraging this investigation, and to other surgical colleagues and nursing staff who suffered appreciable inconvenience in the course of the study. We also thank Denise Gillies for enthusiastic technical assistance and Burroughs Wellcome for supplying atracurium.

## REFERENCES

Abrams, R. E., and Hornbein, T. F. (1975). Inability to reverse pancuronium blockade in a patient with renal failure and hepatic disease. *Anesthesiology*, 42, 362.

Ali, H. H., Utting, J. E., and Gray, T. C. (1971). Quantitative assessment of residual antidepolarising block (Part I). *Br. J. Anaesth.*, 43, 473.

Berry, F. R., and Benson, D. J. (1979). Renal impairment and prolonged curarisation. *Anaesth. Intens. Care*, 7, 192.

Buzello, W., and Agoston, S. (1978). Comparative clinical pharmacokinetics of tubocurarine, gallamine, alcuronium and pancuronium. *Anaesthesist*, 27, 313.

Fahey, M. R., Morris, R. B., Miller, R. D., Sohn, Y. N., Cronnelly, R., and Gencarelli, P. (1981). Clinical pharmacology of Org NC45 (Norcuron). *Anesthesiology*, 55, 6.

Fairley, H. B. (1950). Prolonged intercostal paralysis due to a relaxant. *Br. Med. J.*, 2, 986.

Feldman, S. A., and Levi, J. A. (1963). Prolonged paresis following gallamine. *Br. J. Anaesth.*, 35, 804.

Geha, D. G., Blitt, C. D., and Moon, B. J. (1976). Prolonged neuromuscular blockade with pancuronium in the presence of acute renal failure: A case report. *Anesth. Analg. (Cleve.)*, 55, 343.

Havill, J. M., Mee, A. D., Wallace, M. R., Chin, L. S., and Rothwell, R. P. G. (1978). Prolonged curarisation in the presence of renal failure. *Anaesth. Intens. Care*, 6, 234.

d'Hollander, A., Camu, F., and Sanders, M. (1978). Comparative evaluation of neuro-muscular blockade after pancuronium administration in patients with and without renal failure. *Acta Anaesthesiol. Scand.*, 22, 21.

Hughes, R., and Chapple, D. J. (1981). The pharmacology of atracurium; a new competitive neuromuscular blocking agent. *Br. J. Anaesth.*, 53, 31.

Hunter, J. M., Jones, R. S., and Utting, J. E. (1982a). The use of the muscle relaxant atracurium in anephric patients: a preliminary communication. *J. R. Soc. Med.*, 75, 336.

——— ——— ——— (1982b). Use of atracurium during general surgery monitored by the train-of-four stimuli. *Br. J. Anaesth.*, 54, 1243.

Logan, D. A., Howie, H. B., and Crawford, J. (1974). Anaesthesia and renal transplantation: An analysis of 56 cases. *Br. J. Anaesth.*, 46, 69.

Miller, R. D., and Cullen, D. J. (1976). Renal failure and postoperative respiratory failure: recurarization? *Br. J. Anaesth.*, 48, 254.

—— Stevens, W. C., and Way, W. L. (1973). The effect of renal failure and hyperkalemia on the duration of pancuronium neuromuscular blockade in man. *Anesth. Analg. (Cleve.)*, 52, 661.

Morgan, M., and Lumley, J. (1975). Anaesthetic considerations in chronic renal failure. *Anaesth. Intens. Care*, 3, 218.

Payne, J. P., and Hughes, R. (1981). Evaluation of atracurium in anaesthetized man. *Br. J. Anaesth.*, 53, 45.

Riordan, D. D., and Gilbertson, A. A. (1971). Prolonged curarisation in a patient with renal failure. *Br. J. Anaesth.*, 43, 506.

Rouse, J. M., Galley, R. L. A., and Bevan, D. R. (1977). Prolonged curarisation following renal transplantation. *Anaesthesia*, 32, 247.

Singer, M. M., Dutton, R., and Way, W. L. (1971). Untoward results of gallamine administration during bilateral nephrectomy: Treatment with haemodialysis. *Br. J. Anaesth.*, 43, 404.

Strunin, L. (1966). Some aspects of anaesthesia for renal homotransplantation. *Br. J. Anaesth.*, 38, 812.

White, R. D., DeWeerd, J. H., and Dawson, B. (1971). Gallamine in anesthesia for patients with chronic renal failure undergoing bilateral nephrectomy. *Anesth. Analg. (Cleve.)*, 50, 11.

Wyant, G. M. (1967). The anaesthetist looks at tissue transplantation: Three years' experience with kidney transplants. *Can. Anaesth. Soc. J.*, 14, 255.

## UTILISATION DE L'ATRACURIUM CHEZ LES SUBJETS ANURIQUES

### RESUME

De l'atracurium a été administré chez 26 patients anuriques. Chez 21 d'entre eux, le bloc neuromusculaire a été surveillé en utilisant le stimulus du train de quatre. Les résultats sont comparés à ceux obtenus chez des patients normaux devant être opérés. A l'inverse de ce qui se passe avec les myorelaxants non dépolarisants, habituellement utilisés de nos jours, il a été possible de poursuivre l'administration de doses successives d'atracurium aux sujets anuriques sans observer d'accumulation. Même lorsque la dose totale utilisée (sur une période atteignant 2 h 30) était de l'ordre de sept à huit fois celle antérieurement définie comme le minimum nécessaire à l'intubation endotrachéale (2,3 mg kg$^{-1}$ contre 0,3 mg kg$^{-1}$), il n'y avait pas de signes de curarisation résiduelle. Ce résultat semble compatible avec ce que l'on connait de la pharmacologie du produit. On n'a pas pû mettre en évidence d'effets secondaires hémodynamiques. Nous en concluons que l'atracurium peut être particulièrement intéressant chez les sujets anuriques.

## VERWENDUNG VON ATRAKURIUM BEI PATIENTEN OHNE NIERENFUNKTION

### ZUSAMMENFASSUNG

Atrakurium wurde 26 Patienten die keine Nierenfunktion hatten, verabreicht. Bei 21 von ihnen wurde der neuromuskuläre Block mit Hilfe der "train-of-four" Reizmethode überwacht. Die Ergebnisse werden mit denen von gesunden Patienten, die sich einer Operation unterziehen mußten, verglichen. Im Gegensatz zu den anderen Muskelrelaxantien, die gegenwärtig in Gebrauch sind, war es möglich, den Patienten, die keine Nierenfunktion besaßen, fortgesetzt ansteigende Dosen von Atrakurium zu verabreichen, ohne daß Anzeichen für Akkumulation eintraten. Sogar wenn die verwendete Gesamtmenge (über eine Zeitspanne von länger als 2,5 h) das 7 bis 8-fache der vorher zur endotrachealen Intubation beschriebenen Mindestmenge war (2,3 mg kg$^{-1}$ im Gegensatz zu 0,3 mg kg$^{-1}$), waren keine Zeichen für eine Restrelaxierung vorhanden. Diese Ergebnisse sind mit dem zu vereinbaren, was bisher über die Pharmakologie dieser Substanz bekannt ist. Es zeigten sich keine unerwünschten kardiovaskulären Nebenwirkungen. Daraus wird geschlossen, daß Atrakurium besonders wertvoll für Patienten ohne Nierenfunktion ist.

## USO DEL ATRACURIO EN PACIENTES SIN FUNCION RENAL ALGUNA

### SUMARIO

Se administró atracurio a 26 pacientes que no tenían función renal alguna; en 21 de ellos, el bloqueo neuromuscular fue controlado mediante los estímulos en serie de cuatro. Se hace una comparación entre los resultados obtenidos en pacientes normales sometidos a cirujía y ésos. Al inverso de los agentes relajadores musculares no-depolarizantes usados comúnmente, fue posible administrar dosis crecientes de atracurio a pacientes anefréticos sin que se produjera alguna cumulación. Aún en casos en que la dosis total usada (sobre un periodo de hasta 2,5 horas) correspondía a siete u ocho veces las previamente indicadas como mínimo requerido para intubación endotraqueal (2,3 mg kg$^{-1}$ frente a 0,3 mg kg$^{-1}$), no hubo ninguna señal de curarización residual. Este resultado parece compatible con lo que se sabe de la farmacología de la substancia. No se manifestaron efectos cardiovasculares adversos. Se concluye que el atracurio puede ser especialmente valioso con pacientes que no tenían función renal alguna.

*Br. J. Anaesth.* (1982), 54, 1259

# DOSE–EFFECT RELATIONSHIPS OF EXTRADURAL MORPHINE

D. A. PYBUS AND T. A. TORDA

## SUMMARY

The effectiveness of three different doses of extradural morphine (4, 6 and 8 mg) in relieving post-operative pain was compared in 24 patients. Although there was no significant difference in the efficacy of the three doses, increasing dosage increased the average duration of analgesia provided by the drug (4 mg—593 min; 6 mg—722 min; 8 mg—885 min). All three doses increased the average peak expiratory flow rate, the greatest increases being seen at the higher dosages. Increasing dosage was not accompanied by an increase in the occurrence of adverse effects.

There are now numerous reports in the literature describing the effectiveness of extradural morphine in relieving post-operative pain (Magora et al., 1980; Bromage, Camporesi and Chestnut, 1980; Torda and Pybus, 1981). Although there appears to be a uniformity of opinion regarding the efficacy of the technique, there is no agreement as to what constitutes the optimal dose of the drug when administered in this fashion. Whereas the early investigators (Behar et al., 1979) recommended a dose of 2–3 mg, the more recent trend has been towards using higher doses in the range 5–10 mg (Bromage, Camporesi and Chestnut, 1980; Weddel and Ritter, 1980). The present study was devised to explore the dose–effect relationships of extradural morphine with particular reference to the duration and quality of analgesia and to the physiological effects produced by differing doses of the drug.

## MATERIALS AND METHODS

As with a previous study (Torda and Pybus, 1982) the design adopted was that of a "within patient" controlled trial, which had been approved by the Clinical Trials Committee of our hospital. All the participating patients were admitted to the Intensive Care Unit following major thoracic or abdominal surgery and all gave their informed consent to be studied. In each patient, three different doses of extradural morphine (4, 6 and 8 mg diluted to 10 ml in normal saline) were compared.

In order to eliminate effects of the order of administration of the various doses, each of the six possible sequences of administration of the three doses was given to four patients, so that in all, 24 patients were required to complete the study. In order to complete these 24 studies, 57 studies were attempted:

In 2 patients the trial was abandoned because of a sudden deterioration in their condition which was unrelated to the method of analgesia (post-operative haemorrhage, cardiac arrest). In 9 patients only a single dose of extradural morphine was required so no useful data were derived.

In 19 patients, incomplete data were recorded either because they were discharged from Intensive Care before completion of the study (4) or because four doses of analgesic were not required (15). In another 3 patients doses were administered in incorrect order. Data from these 22 patients are recorded in table II, as "incomplete trials".

In the 24 completed studies, there were 14 males and 10 females and these patients ranged in age from 17 to 72 years and in weight from 35 to 90 kg. Following opiate premedication in all patients, general anaesthesia was induced with thiopentone and maintained with nitrous oxide in oxygen, supplemented by a muscle relaxant and intermittent doses of fentanyl. In some patients, halothane was also used. Extradural catheters were inserted at a spinal level appropriate to the surgery performed, either under anaesthesia or shortly after arrival in the Intensive Care Unit. In seven patients, who underwent major urological surgery, the catheters were at the L2–3 or L3–4 level, and these patients were given extradural bupivacaine during the course of surgery. In the remaining 17 patients the catheters were placed between T4 and T10 and no local

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anaesthetic was used unless there was doubt about the placement of the catheter. In these latter cases, 5 ml of 2% lignocaine was administered and the patient subsequently tested for a band of sensory loss. As soon as the patient complained of pain, he was given an extradural injection of 4, 6 or 8 mg of morphine sulphate diluted to 10 ml in normal saline. The patients were told that the injection would take 45 minutes to achieve a maximal effect and that thereafter they would be given further doses at their request. Immediately before and 45–60 minutes after the injection observations of vital signs and peak expiratory flow rate (PEFR) were made.

The severity of the patients' pain was scored according to a simple scale shown in table I. Complaints of nausea, itching and the occurrence of urinary retention or of vomiting were noted, as were other adverse effects attributable to the technique.

The data were analysed using the following techniques: the durations of action of the three doses were compared using the Mann Whitney rank sum test. The values of the vital signs and PEFR before and after drug administration were analysed using the paired $t$ test. The differences between the effects of the three doses were contrasted using the $t$ statistic for two samples. The significance of differences in the pain scores was assessed using the "Chi squared" test. Correlations between age, weight and duration of analgesia provided by the various doses were tested by the product-moment formula. In all cases findings were considered significant if $P < 0.05$.

## RESULTS

When the trial group alone was considered, the mean duration of action of a 4 mg dose of morphine was 593 minutes, 6 mg, 722 minutes and 8 mg, 885 minutes. The duration of analgesia provided by the 4 mg dose was significantly shorter than that provided by the 8 mg dose, but no other difference was significant. In the 22 patients in whom the trial was not completed the mean duration of action of each dose was longer than in those who completed the trial, but the difference was not significant. When the two groups were combined, the results again did not differ significantly from the completed trials (table II).

TABLE I. *Definition of pain score system used*

| Definition | Score |
|---|---|
| No pain on coughing | 0 |
| Pain on coughing but not on deep breathing | 1 |
| Pain on deep breathing but not at rest | 2 |
| Some pain at rest but desires no other analgesia | 3 |
| Pain at rest, desires more analgesia | 4 |

As expected, the mean duration of action of the first dose, 601 minutes, was shorter than that of the second, 667 minutes, which in turn was shorter than that of the third dose of morphine, 933 minutes. The difference between the first and third doses was significant ($P < 0.05$).

The effects of the three doses on heart rate, respiration, arterial pressure and PEFR are shown in table III.

Heart rates were not significantly altered by any

TABLE II. *Duration of analgesia following the three doses of extradural morphine. *Significantly different from 4 mg,* $P < 0.05$

| Duration (min) | 4 mg | 6 mg | 8 mg |
|---|---|---|---|
| Completed trials | | | |
| Mean (No.) | 593 (24) | 722 (24) | 885* (24) |
| Range | 115–1980 | 180–2100 | 240–1980 |
| Incomplete trials | | | |
| Mean (No.) | 840 (5) | 857 (16) | 1194 (8) |
| Range | 360–1745 | 270–1305 | 360–1620 |
| All trials | | | |
| Mean (No.) | 641 (29) | 776 (40) | 962* (32) |
| Range | 115–1980 | 180–2100 | 240–1980 |

TABLE III. *Changes in vital signs and PEFR before and 45–60 minutes after the three doses of morphine.* *$P < 0.05$. **$P < 0.01$

| | 4 mg | 6 mg | 8 mg |
|---|---|---|---|
| Respiratory rate (b.p.m.) | | | |
| Before | 20.5±4.1 | 22.5±4.2 | 20.7±3.1 |
| After | 19.6±3.3 | 20.9±3.9* | 19.2±2.8* |
| Heart rate (beat $\text{min}^{-1}$) | | | |
| Before | 98±16 | 99±17 | 95±18 |
| After | 97±15 | 100±17 | 98±14 |
| Systolic pressure (mm Hg) | | | |
| Before | 139±25 | 143±38 | 134±28 |
| After | 134±22* | 131±22* | 135±28 |
| Diastolic pressure (mm Hg) | | | |
| Before | 73±11 | 73±15 | 69±15 |
| After | 71±10 | 71±13 | 69±14 |
| Peak expiratory flow rate (litre $\text{min}^{-1}$) | | | |
| Before | 171±94 | 154±70 | 165±89 |
| After | 185±88 | 186±92** | 197±104** |

of the three doses. All doses reduced the mean respiratory rate slightly, but in only the 6 and 8 mg dosage was this reduction significant. The decrease in respiratory rate was generally slight and in no patient was a rate less than 14 per minute recorded. Systolic arterial pressure was unaffected by the 8 mg dose of morphine, but was statistically significantly reduced by the 4 and 6 mg doses. In these latter groups, the mean reduction of systolic pressure was less than 10 mm Hg. The largest recorded decrease in any individual was from 210 mm Hg to 155 mm Hg. There was no significant effect on diastolic arterial pressure. PEFR increased following all three dosages, and this increase was significant ($P < 0.01$) following the 6 and 8 mg doses.

There was no significant difference between the pain scores recorded following the three doses of morphine (fig. 1). Of the 72 observations of pain score in the 24 "trial completed" patients, there were 15 scores of 3 in 9 patients and no scores of 4 were recorded. Three of the patients had scores of 3 throughout the trial, one patient scored 3 on two doses and four patients scored 3 on one dose only.

The duration of analgesia provided by the various doses did not correlate with either the age or weight of the patients.

Among the 24 patients who completed the trial the following side-effects were noted. Nausea and vomiting occurred in one patient only, after arrival in the Intensive Care Unit. She vomited after the first and second opiate doses (4 and 6 mg), but not after the third. Two patients complained of itching, diminished but not completely relieved by naloxone in one and promethazine in the other. The patient given naloxone complained of feeling restless and unwell after its administration. Eight patients of the 24 arrived in the Unit without bladder catheters. Two of these patients, who had undergone thoracotomy and had extradural catheters inserted at T5–6, developed retention and required catheters. One had received 6, the other 8 mg morphine.

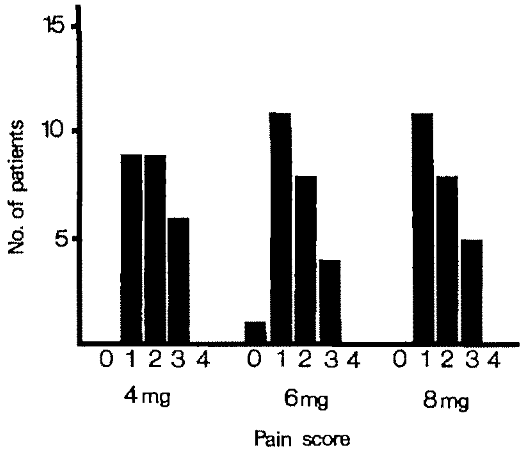

FIG. 1. Histogram showing pain score distribution 45 to 60 minutes after the administration of each of the three (4 mg, 6 mg and 8 mg) doses of extradural morphine.

## DISCUSSION

Before discussion of the results presented, there are three points pertaining to methods which require mention. First, the "Latin Square" design appears to be justified by the demonstrated increase in duration of action of the second and third doses. Had a random design been used it would have been possible that a bias because of the order of administration of the three doses could have affected the result. In a sample as small as this study, it would have been serendipitous had an equal representation of the three doses appeared in a randomized sequence of three administrations.

The second point for discussion concerns the effect of the subjects who failed to complete the trial. The possibility exists that these subjects could bias the results by excluding those who obtained the longest period of pain relief. Comparison of the mean durations for the "trial completed" group and "all trials" demonstrates that this effect was minor.

We also wish to draw attention to the pain score system used in this study. The end-points are objectively defined and very easy to apply to subjects who have pain on breathing. Apart from the authors, three Resident Medical Officers and several nursing staff recorded observations and appeared to do so with a high degree of reproducibility. We suggest that this scoring system offers advantages over those previously described for the study of post-operative pain following abdominal or thoracic surgery. The system has proved particularly useful in patients who cannot co-operate in scoring a visual analogue scale.

Although initially a dose of only 2 mg was used in our unit (Torda, 1979), it soon became apparent that in patients with post-operative pain the quality of relief offered by a 4 mg dose was obviously better (Torda and Pybus, 1981). As there was no increase noted in liability to adverse effects, it was not considered ethically justifiable to explore the dose range below 4 mg. Our findings now indicate that a 4 mg dose of extradural morphine is as efficacious as 6 or 8 mg in relieving post-operative pain in patients not accustomed to opiates. Fifteen (62.5%) of the patients were pain free at rest for the duration of the trial period (except for short intervals at "top-up" time) and a further 6 were pain free at rest following at least one of the doses. Increasing the dose from 4 to 8 mg, did however increase the duration of analgesia, and the PEFR without any apparent increase in the frequency of adverse effects, respiratory, circulatory or otherwise. These results appear to indicate that 4 mg is probably capable of saturating the analgesic receptors available to extradurally administered morphine. The findings of this study should not be applied to patients tolerant to narcotic analgesics who, in our experience, tolerate and require larger doses.

### ACKNOWLEDGEMENTS

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### REFERENCES

Behar, M., F., Olshwang, D. and Davidson, J. T. (1979). Epidural morphine in treatment of pain. *Lancet*, 1, 527.

Bromage, P. R., Camporesi, E. and Chestnut, D. (1980). Epidural narcotics for post-operative analgesia. *Anesth. Analg. Cleve.*, 59, 473.

Magora, F., Olshwang, D., Eimerl, D., Shorr, J., Katzenelson, R., Cotev, S. and Davidson, J. T. (1980). Observations on extradural morphine analgesia in various pain conditions. *Br. J. Anaesth.*, 52, 247.

Torda, T. A. (1979). Epidural analgesia with morphine—a preliminary communication. *Anaesth. Intens. Care*, 7, 367.

—— Pybus, D. A. (1981). Clinical experience with epidural morphine. *Anaesth. Intens. Care*, 9, 129.

—— —— (1982). Comparison of four opiates for extradural analgesia. *Br. J. Anaesth.*, 54, 291.

Weddel, S. J. and Ritter, R. R. (1980). Epidural morphine: serum levels and pain relief. *Anesthesiology*, 53S, 419.

## RELATIONS DOSES–EFFETS DE LA MORPHINE PAR VOIE PERIDURALE

### RESUME

L'efficacité, pour soulager la douleur post-opératoire, de trois doses différentes de morphine, administrées par voie péridurale (4, 6 et 8 mg), a été comparée chez 24 patients. Bien qu'il n'y ait pas eu de différences significatives dans l'efficacité des trois doses, l'augmentation de la posologie s'accompagnait d'une augmentation de la durée moyenne de l'analgésie procurée par le produit (4 mg—593 min; 6 mg—722 min; 8 mg—885 min). Les trois posologies augmentaient la vitesse moyenne du débit expiratoire de pic, l'augmentation maximale étant obtenue avec les plus fortes posologies. L'augmentation des posologies ne s'accompagnait pas d'une augmentation de la fréquence des effets secondaires.

## DOSIS-WIRKUNGSBEZIEHUNG VON EPIDURALEM MORPHIUM

### ZUSAMMENFASSUNG

Die Wirksamkeit von drei verschiedenen Dosen von epidural verabreichtem Morphium in der postoperativen Schmerzbekämpfung wurde an 24 Patienten verglichen. Obwohl kein signifikanter Unterschied in der Wirksamkeit der drei Dosen bestand, führten zunehmende Dosen zu einer Verlängerung der durchschnittlichen Wirkungsdauer der Analgesie (4 mg–593 min; 6 mg–722 min; 8 mg–885 min). Alle drei Dosen vergrößerten die durchschnittliche Spitzenexspirationsrate, wobei die höchsten Anstiege bei den höheren Dosen zu sehen waren. Höhere Dosierung ging nicht mit einer Zunahme unerwünschter Nebenwirkungen einher.

## RELACIÓN DOSIS-EFECTO DE LA MORFINA EPIDURAL

### SUMARIO

Se llevó a cabo una comparación de la eficacia de tres dosis distintas de morfina epidural (4, 6 y 8 mg) para aliviar los dolores postoperatorios. Aunque no hubo diferencia alguna en la eficacia de las tres dosis, la dosificación creciente hizo aumentar la duración media de la analgesia de la substancia (4 mg–592 min; 6 mg–722 min; 8 mg–885 min). Las tres dosis hicieron aumentar el ritmo de la corriente expiratoria tope media, ocurriendo los mayores aumentos con las dosis más elevadas. La dosificación creciente no se acompañó por un aumento de la ocurrencia de efectos adversos.

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# POSTOPERATIVE ANALGESIA AFTER CIRCUMCISION IN CHILDREN

L.V.H. MARTIN

## SUMMARY

The analgesic effects of systemically administered diamorphine, caudal analgesia with 0.5% bupivacaine plain and caudal analgesia with 0.5% bupivacaine plain to which morphine sulphate had been added were studied in boys undergoing circumcision. Postoperative analgesia was assessed using a linear analogue scale. The time interval between operation and subsequent analgesic administration and the number of analgesic doses in 24 h were compared. The frequency of vomiting was noted. All three methods provided satisfactory results. The only detectable difference between the groups was a more rapid, but transient, recovery in the group receiving plain bupivacaine only. The frequency of vomiting was high in all groups. Caudal analgesia, with or without the addition of morphine, did not confer any advantage over injected diamorphine, and did not justify the extra time, risk and expense required to carry it out.

For some years the author has used a technique based on the administration of diamorphine during operation to provide postoperative analgesia after circumcision, with satisfactory results. Caudal analgesia has been recommended (Kay, 1974) and its use was found to provide results which were good, but not strikingly better than, the diamorphine technique. More recently, prolonged analgesia has been reported in adults following the introduction of small doses of opiates into the extradural space (Behar et al., 1979).

This survey is intended to investigate whether caudal analgesia is superior to systemically administered diamorphine and whether the addition of morphine to the local analgesic solution confers any benefit.

## METHODS

Sixty boys admitted consecutively to hospital from the waiting list for circumcision were randomly allocated to one of three groups. On the day of operation all received premedication consisting of diazepam 0.22 mg kg$^{-1}$ and hyoscine 0.01 mg kg$^{-1}$ by mouth approximately 2 h before operation. Induction of anaesthesia was with thiopentone 4 mg kg$^{-1}$ or by the inhalation of nitrous oxide, oxygen and halothane according to size or the child's stated preference. Anaesthesia was maintained with 70% nitrous oxide in oxygen, with 1% halothane.

The first group received diamorphine 0.07 mg kg$^{-1}$ in two increments. A small dose, up to 0.5 mg, was given slowly i.v. during the early part of the operation and the remainder of the dose was given i.m. when surgery had been completed. The diamorphine was diluted to a solution containing 1 mg ml$^{-1}$ in order that small doses could be handled accurately.

After anaesthesia had been induced, the second group received a caudal injection of 0.5% bupivacaine plain using a dose of 0.5 ml per year as recommended by Kay (1974), and corresponding to the 0.1 ml per spinal segment per year suggested by Schulte-Steinberg and Rahlfs (1977).

Morphine sulphate 2 mg was added to 10 ml of 0.5% bupivacaine plain and the third group received a caudal injection of this solution using the same age-related volumes as in the previous group. This dosage of morphine was arrived at from the 2 mg of morphine sulphate in 10 ml of saline reported to be effective in adults in the lumbar extradural space (Behar et al., 1979).

Anaesthesia was maintained until surgery had ended and the last stitch had been inserted.

After the operation children were assessed on a linear analogue scale by the paediatric ward sister and a small number of staff nurses under her supervision. The zero end of the scale represented the anaesthetized child and the 10-cm end a child who was screaming and uncontrollable, with a child who was awake, alert and pain-free being recorded near the 50-mm mark. Assessments were made at 5-min intervals for the 1st hour, 15-min intervals for the 2nd hour, and hourly thereafter for a further 4 h.

If the children required further analgesia they

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received elixir of paracetamol by mouth. The time from the end of the operation to the administration of the first dose of paracetamol was noted, as was the number of doses required in the first 24 h. The number of episodes of vomiting in the first 24 h was recorded.

## RESULTS

The characteristics of the three groups are shown in table I and it will be seen that they are comparable.

Figure 1 shows the linear analogue results. The patients in the diamorphine group were considered to be sufficiently recovered to return to the ward 15–20 min after the end of anaesthesia. They remained asleep for the 1st hour and thereafter they wakened gradually and were fully recovered by the end of 4 or 5 h.

TABLE I. *Patient characteristics (mean ± SEM)*

|  | *n* | Age (yr) | Height (cm) | Weight (kg) |
|---|---|---|---|---|
| Diamorphine | 20 | 6.5<br>±0.28 | 116.66<br>±3.21 | 21.95<br>±1.26 |
| Caudal 0.5% bupivacaine plain | 20 | 6.0<br>±0.67 | 113.95<br>±4.19 | 24.23<br>±2.44 |
| Caudal 0.5% bupivacaine plain with morphine | 20 | 5.6<br>±0.69 | 109.89<br>±4.57 | 22.05<br>±2.78 |

The group who had received a caudal injection of bupivacaine with the addition of morphine followed a similar course.

The results were different in the group receiving the caudal injection with bupivacaine alone. There were two complete failures in this group and diamorphine had to be given in the ward because of distress. One was a technical failure occasioned by anatomical abnormality and the other occurred in a small child in whom there was emotional disturbance. The remaining 18 were more lively on return to the ward and remained so until the end of the 1st hour, when they rejoined the other two groups and followed a similar course thereafter. The difference between this group and the diamorphine group was significant at 30, 35 and 40 min only.

Table II shows subsequent analgesic requirements and the frequency of vomiting. There is no significant difference between the groups as regards time to first analgesia, number of analgesic doses required in the first 24 h or the occurrence of vomiting.

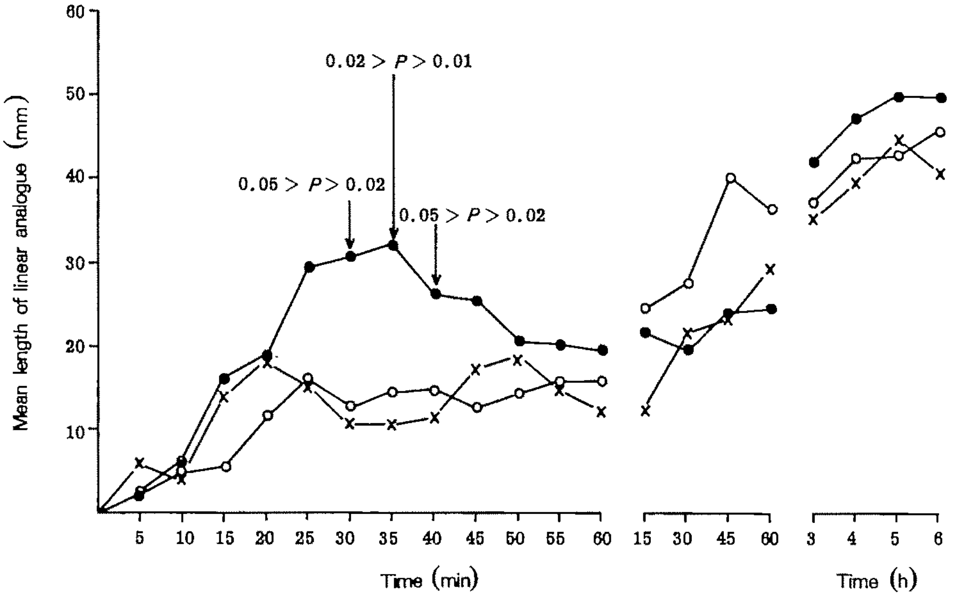

FIG. I. Mean length of linear analogue plotted against time for the three groups. × = Diamorphine; ● = 0.5% bupivacaine plain; ○ = 0.5% bupivacaine plain with morphine.

TABLE II. *Analgesic requirements and frequency of vomiting in 24 h after operation*

| | *n* | Time to first analgesia (h) (mean ± SEM) | Number of patients receiving analgesia | | | Number of patients vomiting | | |
|---|---|---|---|---|---|---|---|---|
| | | | None | One dose | Two or more doses | None | Once | Two or more times |
| Diamorphine | 20 | 13.72<br>±1.42 | 7 | 10 | 3 | 10 | 5 | 5 |
| Caudal 0.5% bupivacaine plain | 18 | 10.23<br>±1.47 | 6 | 6 | 6 | 13 | 3 | 2 |
| Caudal 0.5% bupivacaine plain with morphine | 20 | 9.74<br>±1.37 | 6 | 8 | 6 | 10 | 6 | 4 |

## DISCUSSION

All the methods were found to give satisfactory results although there was a high frequency of vomiting in all groups. The only detectable difference between the groups was a more rapid recovery in the patients receiving the plain caudal injection, but this advantage had been lost by the end of the 1st hour. The small dose of morphine used caudally did not produce prolonged analgesia, but did appear to have an early sedative effect. In the volumes used it is unlikely that the solution would reach the spinal cord, even in children, and any effect would be the result of systemic absorption. The results obtained can be explained on this basis.

It would appear from this survey that caudal injections of local anaesthetics, with or without the addition of morphine, do not have any advantages over systemically administered diamorphine when given in the manner described and do not warrant the extra time, risk and expense of performing them.

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### REFERENCES

Behar, M., Magora, F., Olshwang, D., and Davidson, J.T. (1979). Epidural morphine in treatment of pain. *Lancet*, 1, 527.

Kay, B. (1974). Caudal block for post-operative pain relief in children. *Anaesthesia*, **29**, 610.

Schulte-Steinberg, O., and Rahlfs, V. W. (1977). Spread of extradural analgesia following caudal injection in children. *Br. J. Anaesth.*, **49**, 1027.

## ANALGESIE POST-OPERATOIRE APRES CIRCONCISION CHEZ L'ENFANT

### RESUME

On a étudié les effets analgésiques de diamorphine administrée par voie parentérale, d'une analgésie caudale avec de la bupivacaïne simple à 0,5% et d'une analgésie caudale avec de la bupivacaïne simple à 0,5% à laquelle avait été ajoutée du sulfate de morphine, chez des garçonnets subissant une circoncision. L'analgésie post-opératoire était étudiée en utilisant une échelle analogue linéaire. On a comparé l'intervalle de temps entre l'intervention et l'administration suivante d'analgésique et le nombre de doses d'analgésique reçues en 24 h. La fréquence des vomissements a été notée. Les trois méthodes ont fourni des résultats satisfaisants. La seule différence décelable entre les groupes était un réveil plus rapide mais transitoire dans le groupe qui ne recevait que de la bupivacaïne simple. La fréquence des vomissements était élevée dans tous les groupes. L'analgésie caudale, avec ou sans adjonction de morphine, n'a présenté aucun avantage par rapport aux injection de diamorphine, et ne justifie pas la perte de temps, les risques et la dépense supplémentaire qu'elle comporte.

## POSTOPERATIVE ANALGESIE NACH ZIRKUMZISION BEI KINDERN

### ZUSAMMENFASSUNG

Die analgetische Wirkung von systemisch verabreichtem Diamorphin, Kaudalanästhesie mit 0,5% Bupivakain einfach und Kaudalanästhesie mit 0,5% Bupivakain einfach, dem Morphiumsulphat zugefügt worden war, wurde an Jungen untersucht, die sich einer Zirkumzision unterziehen mußten. Die Bestimmung der postoperativen Analgesie erfolgte mittels einer linearen Analogskala. Der Zeitabstand zwischen Operation und darauffolgender Analgetikagabe und die Anzahl der Analgetikagaben in 24 Stunden wurden verglichen und die Häufigkeit des Erbrechens festgehalten. Alle drei Methoden ergaben zufriedenstellende Ergebnisse. Der einzige Unterschied,

der zwischen den Gruppen zu entdecken war, war eine schnellere, aber vorübergehende Erholung in der Gruppe mit nur einfachem Bupivakain. Die Häufigkeit von Erbrechen war in allen Grüppen hoch. Die Kaudalanästhesie, mit oder ohne Zusatz von Morphium, zeigte überhaupt keinen Vorteil gegenüber injiziertem Diamorphin, und rechtfertigte nicht den zu ihrer Durchführung nötigen Zeitaufwand, das Risiko und die Kosten.

## ANALGESIA POSTOPERATORIA DESPUES DE CIRCUNCISIÓN EN NIÑOS

### SUMARIO

Se llevó a cabo un estudio de los efectos analgésicos en niños sometidos a circuncisión de la diamorfina sistémicamente administrada, de la analgesia caudal con bupivacaina llana al 0,5% y de la analgesia caudal con bupivacaina llana al 0,5% a la cual se añadió sulfato de morfina. Se evaluó la analgesia post-operatoria mediante una escala análoga linear. El intervalo de tiempo entre la operación y la administración analgésica subsecuente y el número de dosis analgésicas durante 24 h fueron objeto de un estudio comparativo. Se observó la frecuencia del vómito. Los tres métodos dieron resultados satisfactorios. La única diferencia discernible entre los grupos consistió en una recuperación más rápida, pero transitoria, en el grupo al cual se administró la bupivacaina simple solamente. Fue alta la frecuencia del vómito en los tres grupos. La analgesia caudal, con o sin adición de morfina, no confirió ventaja alguna con respecto a la diamorfina inyectada y no justificó el tiempo adicional, el riesgo y los gastos necesarios a su administración.

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# FENTANYL PHARMACOKINETICS IN ANAESTHETIZED PATIENTS WITH CIRRHOSIS

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AND P. DUVALDESTIN

## SUMMARY

Fentanyl kinetics were studied in patients with cirrhosis and in patients with normal hepatic and renal function undergoing surgery under general anaesthesia, the latter group served as the controls. Plasma fentanyl concentrations declined bi-exponentially in the controls with an average elimination half-life ($T_{\frac{1}{2}}^{\beta}$) of 263 min; total plasma clearance (*Cl*) was 10.8 ml min$^{-1}$ kg$^{-1}$, and total apparent volume of distribution ($V^{\beta}$) 3.81 litre kg$^{-1}$. No significant change was observed in patients with cirrhosis: $T_{\frac{1}{2}}^{\beta}$ was 304 min, *Cl* 11.3 ml min$^{-1}$ kg$^{-1}$ and $V^{\beta}$ 4.41 litre kg$^{-1}$. These data suggest that the elimination half-life of fentanyl is not primarily influenced by the rate at which it is metabolized in the liver.

The liver is the primary organ responsible for the elimination of fentanyl. In patients with cirrhosis, it remains however difficult to predict whether the hepatic dysfunction will result in retarded fentanyl kinetics. Our study was designed to investigate the pharmacokinetics of fentanyl after a single intravenous dose in patients with cirrhosis undergoing surgery under general anaesthesia.

## METHODS

Our subjects were eight patients with liver cirrhosis between the ages of 32 and 73 yr (50 ± 5, mean ± SEM) and weighing 50 to 75 kg (61 ± 4) and 13 patients with normal hepatic and renal function between the ages of 24 and 75 yr (41 ± 5) and weighing 52 to 90 kg (65 ± 3) undergoing surgery under general anaesthesia. Table I summarizes the clinical and laboratory features in the patients with cirrhosis. Alcoholism was the cause of liver disease in all the patients and cirrhosis was confirmed by the histological examination of a liver biopsy. At the

TABLE I. *Characteristics of cirrhotic patients.* a = *Serum glutamic pyruvic transaminase, normal value* < *30 i.u. ml*$^{-1}$. b = *Normal value* < *180 i.u. ml*$^{-1}$

| | | Preoperative liver function tests | | | | | |
|---|---|---|---|---|---|---|---|
| Cirrhotic subject number | Surgical procedure | Serum total protein (g litre$^{-1}$) | Serum albumin (g litre$^{-1}$) | SGPT$^{a}$ (i.u. ml$^{-1}$) | Serum$^{b}$ alkaline phosphatase (i.u. ml$^{-1}$) | Serum bilirubin (μmol litre$^{-1}$) | Prothrombin % of normal |
| 1 | Total hip arthroplasty | 83 | 36 | 40 | 60 | 15 | 80 |
| 2 | Oesophageal transection | 72 | 41 | 72 | 85 | 17 | 56 |
| 3 | Portocaval shunt | 58 | 29 | 37 | 126 | 65 | 29 |
| 4 | Peritoneoscopy | 65 | 34 | 60 | 47 | 29 | 67 |
| 5 | Skin graft | 62 | 25 | 25 | 66 | 15 | 72 |
| 6 | Anal fistulae | 85 | 41 | 28 | 53 | 14 | 61 |
| 7 | Vagotomy | 68 | 30 | 45 | 86 | 56 | 55 |
| 8 | Abdominal herniae | 69 | 31 | 17 | 202 | 18 | 75 |

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time of the study, none of the patients had ingested alcohol during the past 2 weeks and none had ascites. The controls underwent abdominal surgery in six patients and orthopaedic or reconstructive surgery in seven patients. Premedication consisted of atropine 0.5 mg i.m., and diazepam 10 mg, given orally 30 min before anaesthesia.

Anaesthesia was induced with thiopentone 5 to 8 mg kg$^{-1}$ i.v.; suxamethonium 0.8 mg kg$^{-1}$ was given to facilitate tracheal intubation. Anaesthesia was maintained with 60% nitrous oxide in oxygen delivered by mechanical ventilation. Pancuronium 80 $\mu$g kg$^{-1}$, followed by repeated doses of 20 $\mu$g kg$^{-1}$ was given to provide adequate muscle relaxation. A single bolus dose of fentanyl 5 $\mu$g kg$^{-1}$ was given intravenously. In some cases, when the duration of operation exceeded 2 h, phenoperidine which does not interfere with the assay of fentanyl was given in doses varying from 0.5 to 4.5 mg.

Heparinized blood samples were drawn before and at 5, 10, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480 and 600 min after the injection of fentanyl. Plasma was separated immediately and kept frozen at −20 °C until subsequent analysis. Fentanyl in plasma was assayed by radioimmunoassay (Michiels, Hendriks and Heykants, 1977). The lower limit of sensitivity is 25 pg ml$^{-1}$ and the method has a coefficient of variation of 5% for a concentration of 1 ng ml$^{-1}$ in this laboratory. No cross sensitivity of the assay to phenoperidine was observed at phenoperidine concentration, 200 times higher than fentanyl concentration. Fentanyl plasma concentration *v.* time for each patient, were fitted to the biexponential function: $C_P(t) = Ae^{-\alpha t} + Be^{\beta t}$ using a non-linear least squares regression program (Gomeni and Gomeni, 1978). In this expression, $C_P(t)$ is the plasma concentration at time $t$, $A$ and $B$ are constants and alpha and beta are the rapid and slow exponential disposition constants with half-lives $T_{\frac{1}{2}}^{\alpha}$ and $T_{\frac{1}{2}}^{\beta}$, respectively. From these best-fit parameters, $V$ (initial volume of distribution), $V^{\beta}$ (volume of distribution during elimination), $V^{ss}$ (volume of distribution at steady state) and plasma clearance were calculated. In addition, the area under the plasma concentration of fentanyl *v.* time curve ($AUC_{total}$) was also estimated by the trapezoidal rule. Statistical differences between the data obtained in the patients with cirrhosis and in the controls were analysed by the two-tailed non parametric Mann-Whitney *U*-test.

## RESULTS

The plasma concentration/time profiles of fentanyl for control and cirrhotic patients are shown in figures 1 and 2 respectively. The profiles are qualitatively and quantitatively similar. The initial rapid phase of distribution is followed by the elimination phase with half-lives of 263±49 min and 304±74 min (mean±SEM) in controls and cirrhotics respectively (table II). Similar values were found for the different pharmacokinetic parameters between control and cirrhotic patients. No significant difference was observed in the plasma clearance between the two groups (table II).

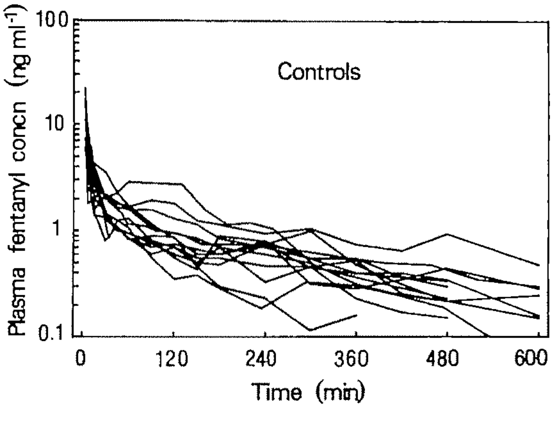

FIG. 1. Fentanyl plasma concentration in 13 surgical patients with normal renal and hepatic function after a single intravenous dose of 5 $\mu$g kg$^{-1}$.

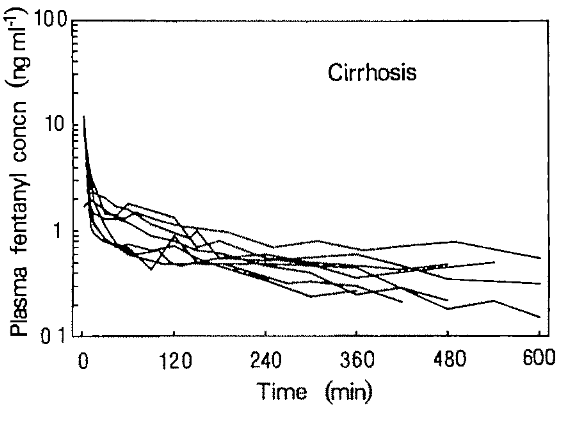

FIG. 2. Fentanyl plasma concentration in 8 cirrhotic patients after a single intravenous dose of 5 $\mu$g kg$^{-1}$.

TABLE II. *Effect of cirrhosis on the disposition and elimination of fentanyl. $V$ = Initial volume of distribution, $V^{\beta}$ = volume of distribution during elimination, $V^{ss}$ = Volume of distribution at steady state, $T_{\frac{1}{2}}^{\alpha}$ = Distribution half-life, $T_{\frac{1}{2}}^{\beta}$ = Elimination half-life, $Cl$ = Plasma clearance,* $\mathrm{AUT_{total}}$ = *Area under the plasma total fentanyl* v. *time concentration curve.* [a]Mean ± SEM, [b]P > *0.2, for all parameters*

| | Controls | Cirrhosis[b] |
|---|---|---|
| $T_{\frac{1}{2}}^{\alpha}$ (min) | 9 ± 3 | 8 ± 4 |
| $T_{\frac{1}{2}}^{\beta}$ (min) | 263 ± 49 | 304 ± 74 |
| $V_1$ (litre $\mathrm{kg^{-1}}$) | 0.77 ± 0.29 | 1.02 ± 0.36 |
| $V^{\beta}$ (litre $\mathrm{kg^{-1}}$) | 3.81 ± 67 | 4.41 ± 72 |
| $V^{ss}$ (litre $\mathrm{kg^{-1}}$) | 3.44 ± 64 | 4.27 ± 65 |
| $Cl$ (ml $\mathrm{min^{-1}\,kg^{-1}}$) | 10.8 ± 1.2 | 11.3 ± 1.6 |
| $\mathrm{AUC_{total}}$ (ng $\mathrm{ml^{-1}\,min^{-1}}$) | 518 ± 53 | 507 ± 63 |

## DISCUSSION

Fentanyl like most lipophilic drugs, is nearly completely metabolized in the liver before it is eliminated and in man was only 6.5% of the dose excreted as unchanged drug in urine (McClain and Hug, 1980). In view of this elimination profile, alteration of its pharmacokinetics especially during the elimination phase is expected in patients with liver disease. However this study indicates that the pharmacokinetics of fentanyl are not altered in surgical patients with cirrhosis.

These results contrasted with previous studies of the elimination kinetics of two other central analgesics pethidine and pentazocine which plasma clearances were prolonged in patients with cirrhosis (Klotz et al., 1974; Neal et al., 1979). Several explanations can be discussed for the absence of modification of fentanyl plasma clearance in patients with cirrhosis.

In patients with cirrhosis, three factors modify drug clearance (Wilkinson and Shand, 1975): i) reduced hepatic blood flow; ii) diminished activity of drug metabolizing enzymes; and iii) decreased fraction of plasma protein bound drug. In examining these factors in the content of our study, we note that fentanyl clearance per unit of hepatic blood flow is high in control subjects. This suggests that fentanyl has a high hepatic extraction ratio and that its clearance will be relatively sensitive to changes in hepatic blood flow and insensitive to alterations in metabolic activity. Also, it is known that the extraction ratio of fentanyl largely exceeds the unbound plasma fraction of drug (19% in normal subjects) (McClain and Hug, 1980). Consequently, the plasma clearance will be insensitive to decreased plasma protein binding of fentanyl. Thus, the unchanged clearance of fentanyl which we observed in patients with cirrhosis suggests that hepatic blood flow was not markedly diminished in these patients compared with normal patients. This can also be deduced from the data in table I; none of the patients with cirrhosis had profound hepatic insufficiency. Another explanation for the absence of significant changes in plasma fentanyl clearance in the presence of cirrhosis may be related to the distribution characteristics of fentanyl. Because of the large volume of the peripheral compartment only a small fraction of fentanyl is present in the central compartment and is available for hepatic uptake. It has been suggested by McClain and Hug (1980) that the terminal half-life of fentanyl probably better reflects its slow release from tissue depots than its hepatic elimination.

ACKNOWLEDGEMENTS

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REFERENCES

Gomeni, C., and Gomeni, R. (1978). IGPHARM: Interactive graphic package for pharmacokinetics analysis. *Comp. Biomed. Res.*, **11**, 345.

Klotz, U., McHorse, T. S., Wilkinson, G. R., and Schenker, S. (1974). The effect of cirrhosis on the disposition and elimination of meperidine in man. *Clin. Phamacol. Ther.*, **16**, 667.

McClain, D. A., and Hug, C. C. (1980). Intravenous fentanyl kinetics. *Clin. Pharmacol, Ther.*, **28**, 106.

Michiels, M., Hendriks, R., and Heykants, J. (1977). A sensitive radioimmunoassay for fentanyl. *Europ. J. Clin. Pharmacol.*, **12**, 153.

Neal, E. A., Meffin, P. J., Gregory, P. B., and Blaschke, T. F. (1979). Enhanced bioavailability and decreased clearance of analgesics in patients with cirrhosis. *Gastroenterology*, **77**, 96.

Wilkinson, G. R., and Shand, D. G. (1975). A physiological approach to hepatic drug clearance. *Clin. Pharmacol. Ther.*, **18**, 377.

## PHARMACOCINETIQUE DU FENTANYL CHEZ DES SUJETS CIRRHOTIQUES ANESTHESIES

### RESUME

La pharmacocinétique du fentanyl a été étudiée chez des sujets cirrhotiques et chez des sujets ayant une fonction hépatique et rénale normale, soumis à des actes chirurgicaux sous anesthésie générale, le deuxième groupe servant de témoins. Les concentrations plasmatiques de fentanyl diminuaient de façon bi-

exponentielle chez les contrôlés avec une demi-vie moyenne d'élimination ($T_{\frac{1}{2}}^{\beta}$) de 263 min; la clairance plasmatique totale (*Cl*) était de 10,8 ml kg$^{-1}$ min$^{-1}$ et le volume total apparent de distribution ($V^{\beta}$) de 3,81 litre kg$^{-1}$. Les paramètres des patients atteints de cirrhose n'étaient pas significativement différents: le $T_{\frac{1}{2}}^{\beta}$ était de 304 min, la *Cl* de 11,3 ml kg$^{-1}$ min$^{-1}$ et le $V^{\beta}$ de 4,41 litre kg$^{-1}$. Ces données suggèrent que la demi-vie d'élimination du fentanyl n'est pas influencée, au premier chef, par la vitesse à laquelle il est métabolisé dans le foie.

## DIE PHARMAKOKINETIK VON FENTANYL BEI NARKOTISIERTEN PATIENTEN MIT ZIRRHOSE

### ZUSAMMENFASSUNG

Die Kinetik von Fentanyl wurde an Patienten mit Zirrhose und an Patienten mit normaler Leber- und Nierenfunktion untersucht, die sich einer Operation in Allgemeinnarkose unterziehen mußten, wobei die Patienten mit den normalen Werten als Kontrollgruppe dienten. Die Plasmafentanyl-konzentrationen nahmen in der Kontrollgruppe biexponentiell ab mit einer durchschnittlichen Eliminationshalbwertszeit ($T_{\frac{1}{2}}^{\beta}$) von 263 min; die totale Plasmaclearance (*Cl*) war 10,8 ml min$^{-1}$ kg$^{1-1}$, und das offensichtliche gesamte Verteilungsvolumen ($V^{\beta}$) war 3,81 litre kg$^{-1}$. Bei Zirrhosepatienten war keine signifikante Änderung zu beobachten: $T_{\frac{1}{2}}^{\beta}$ war 304 min, *Cl* 11,3 ml min$^{-1}$ kg$^{-1}$ und $V^{\beta}$ 4,41 litre kg$^{-1}$. Diese Werte lassen darauf schließen daß die Eliminationshalbwertszeit von Fentanyl nicht primär durch die Metabolisierungsrate in der Leber beeinflußt wird.

## FARMACOCINÉTICA DEL FENTANILO EN PACIENTES CON CIRROSIS ANESTESIADOS

### SUMARIO

Se hizo un estudio de la cinética del fentanilo en pacientes padeciendo de cirrosis y en pacientes con función renal y hepática normal sometidos a cirujía bajo anestesia general, este último grupo sirviendo de controles. Las concentraciones de fentanilo en el plasma bajaron exponencialmente en los controles con una media-vida media de eliminación ($T_{\frac{1}{2}}^{\beta}$) de 263 min. La evacuación total del plasma (*Cl*) era de 10,8 ml min$^{-1}$ kg$^{-1}$ y el volumen aparente total de distribución ($V^{\beta}$) de 3,81 litro kg$^{-1}$. Ningún cambio significante fue observado en los pacientes con cirrosis: $T_{\frac{1}{2}}^{\beta}$ era de 304 min, la *Cl* de 11,3 ml min$^{-1}$ kg$^{-1}$ y el $V^{\beta}$ de 4,41 litro kg$^{-1}$. Estos datos hacen pensar que la media vida de eliminación del fentanilo no se halla básicamente influenciada por el ritmo según el cual se metaboliza en el hígado.

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# ACUTE I.V. METHADONE KINETICS IN MAN: RELATIONSHIP TO CHRONIC STUDIES

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## SUMMARY

Twenty-six patients were given methadone 10 mg i.v. to obtain acute human kinetics. Plasma methadone concentrations from separate 3- and 6-h studies were measured by radioimmunoassay. Kinetic parameters derived from triexponential NONLIN analysis showed that $T_{\frac{1}{2}}{}^{\alpha}$ and $T_{\frac{1}{2}}{}^{\beta}$ were 2 and 30 min respectively; no reliable estimate for $T_{\frac{1}{2}}{}^{\gamma}$ could be obtained. The clearance was estimated as 149 ± 62 and 163 ± 49 ml $\text{min}^{-1}$ in the 3- and 6-h studies respectively. These values were compared with those published for chronic administration. The difficulties in determining accurate terminal half-life and clearance values from short duration studies are discussed; these difficulties are accentuated by the long terminal half-life of methadone. Appropriate estimates of clearance may be derived from an acute short duration study provided that the average of triexponential fits to individual patient data is used, even when data extend for only 3 h. As might be anticipated, no analysis produced appropriate terminal half-life values for this drug.

An important role for pharmacokinetics is the prediction of the kinetic consequences of multiple doses of a drug from single-dose studies. Two parameters are of fundamental importance in this respect. The terminal half-life determines the rate of decrease of plasma concentration after dosing and hence the interval between doses, and the clearance determines the steady state plasma concentration around which the dosing variations occur. Both the half-life and the clearance may be derived from the acute i.v. dose curve.

Anaesthetists use the i.v. route routinely and are well placed to determine the acute pharmacokinetics of the drugs which they give. This paper was concerned with the problem of acute studies when the drug has a long terminal half-life. The terminal half-life will be unknown in the early stages of research into a new drug. Some practical considerations then arise. How long should a single-dose study continue in order to provide good estimates of these parameters? Conversely, given perhaps the necessity of a study of finite duration after a single dose, how reliable will the estimates from the acute study be in predicting the values for chronic use of the drug?

The acute i.v. kinetics of methadone provide a good opportunity to investigate this general problem. First, the early phase kinetics of methadone have not been reported. Second, there is a wealth of chronic dosing kinetics available in the literature which can be used to elucidate the general problem.

The present study describes the plasma concentrations and kinetic analysis of methadone after a single 10-mg i.v. bolus dose. Two different clinical situations were used in comparable patient groups.

## PATIENTS AND METHODS

Twenty-six patients undergoing elective total hip replacement were selected sequentially from operating lists at the Nuffield Orthopaedic Centre, Oxford. Approval for the study was obtained from the Hospital Ethics Committee.

Patients selected were of either sex, aged 40–75 yr, of 45–90 kg body weight with normal haematological and biochemical profiles. Those with known cardiovascular, respiratory, hepatic, renal or endocrine disorder, or taking regular medication likely to interfere with the distribution of tissue blood flows were excluded from the study. The patients were randomly assigned to one of two groups, defined by the time when they received the i.v. dose of methadone. The intraoperative group (group I) were given methadone hydrochloride 10 mg i.v. (Physeptone Injection, Wellcome) soon after induction of anaesthesia. The postoperative

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group (group P) received methadone 10 mg i.v. after operation, 3 h later. Both groups received oral lorazepam 2 mg 3 h before operation as premedication. The two groups then had different anaesthetics.

For group I, anaesthesia was induced with thiopentone sodium 5 mg kg$^{-1}$ i.v. followed by pancuronium bromide 0.1 mg kg$^{-1}$. After tracheal intubation, artificial ventilation to normocapnia was continued using 67% nitrous oxide in oxygen with 0.5% halothane, delivered through a Bain circuit at a total fresh gas flow of 70 ml min$^{-1}$ kg$^{-1}$, with a measured expired tidal volume of 10 ml kg$^{-1}$ at 12 b.p.m. Halothane was used to avoid awareness and to suppress autonomic effects on the drug kinetics. A 20-gauge cannula was inserted in the radial artery. Approximately 15 min after induction, methadone 10 mg was given i.v., diluted to 10 ml in 0.9% saline and injected over 60 s into a flowing i.v. infusion; timing for samples began at the end of the injection period. Supplementary doses of pancuronium were not given. Halothane administration was discontinued approximately 15 min before the end of surgery. Residual neuromuscular blockade was antagonized with i.v. atropine 1.2 mg and neostigmine 2.5 mg. Arterial blood samples were taken for estimation of methadone concentrations at 2, 5, 7.5, 10, 20, 30, 40, 60, 80, 100, 120, 150, 180, 210, 240, 270, 300, 330, and 360 min. A baseline venous sample was taken before induction. All blood samples were taken into lithium heparin tubes, centrifuged, and the plasma separated at room temperature. Plasma was stored at −20°C until required for analysis.

For group P, a lumbar extradural was performed before induction and 0.5% plain bupivacaine 15–20 ml was given. After thiopentone sodium 5 mg kg$^{-1}$, anaesthesia was maintained by spontaneous breathing of 67% nitrous oxide in oxygen with 0.5% halothane delivered to a face-mask through a Bain circuit. A 20-gauge cannula was inserted in the radial artery. The administration of halothane and nitrous oxide was discontinued at the end of surgery. After operation (at about 180 min after induction) methadone 10 mg, diluted to 10 ml in 0.9% saline, was injected over 60 s into a flowing i.v. infusion. The timing began at the end of the injection. Arterial blood samples were taken for methadone estimation at 2, 5, 7.5, 10, 20, 30, 40, 60, 80, 100, 120, 150, and 180 min. A baseline venous sample was taken before induction; the samples were treated in the same way as the group I samples.

In both groups, initial fluid replacement was with Hartmann's solution 5 ml h$^{-1}$ kg$^{-1}$ for the first 2 h. This was followed by blood transfusion according to a specific formula. Blood loss during operation was estimated by swab weighing and calibrated suction. All patients were on a warming blanket during anaesthesia, with continuous e.c.g., direct arterial pressure, and nasopharyngeal and peripheral temperature monitoring.

After operation all patients were transferred to the recovery ward where they stayed until the following day, breathing 28% oxygen by Ventimask for the remainder of the study period.

### *Analytical procedures*

Plasma samples were diluted in phosphate buffered saline (pH 7.2) and duplicate 100-μlitre aliquots of the diluent were added to tubes containing approximately 10 000 d/min of (±)-methadone-o, o′-$^3$H (7.4 Ci mmol$^{-1}$, Research Triangle Institute, a gift from the National Institute for Drug Abuse), and methadone antiserum at a final dilution of 1:2500 (a gift from Professor C. Inturrisi) in a final volume of 0.4 ml containing 0.025% bovine serum albumin (BSA). Standards of methadone hydrobromide, and total count and non-specific binding tubes were similarly treated. After incubation for 1 h at room temperature the tubes were placed in ice-slush for 10 min, then 0.5 ml of charcoal/dextran mixture containing activated charcoal 5 mg and Dextran T70 0.5 mg in buffered saline with 0.1% BSA was added. The tubes were shaken in a vortex mixer, incubated in the slush for 12 min and then centrifuged at 3000 *g* for 15 min. Finally a 0.5-ml aliquot of the supernatant was mixed with 2 ml of scintillant (PCS, Amersham) and counted for 5–10 min on a beta counter (LKB Rackbeta).

Tubes with $^3$H-methadone only bound 55.4±1.9% (mean±SEM) of total radioactivity, and the non-specific binding was 14.9±0.99% (mean±SEM). Control samples were assayed on each occasion; plasma pools containing methadone 100 ng ml$^{-1}$ and 50 ng ml$^{-1}$ yielded recoveries of 101.5±1.5 ng ml$^{-1}$ (mean±SEM; coefficient of variation, cv = 6.6%) and 50.8±1.1 ng ml$^{-1}$ (mean±SEM; cv = 9.9%) respectively when assayed in all 21 assays. All plasma concentrations are expressed as methadone base.

### *Analysis of results*

Plasma concentrations were fitted to a sum of exponentials curve using NONLIN (Metzler, Elfring and McEwen, 1974) on the University of

Oxford ICL 2980 computer. Weighting was not used, for the following reasons:

(i) the majority of data points were seen to have very similar variances (table II).

(ii) It is the most straightforward initial option, because it does not involve any manipulations with, or assumptions about, the data. In particular, theoretical fits to the plasma drug decay curve of an individual subject are frequently seen to be inherently good or bad, that is there is some correlation between deviations from the fit within the individual. This may relate to experimental circumstances within that individual, such as instability of tissue blood flows. Weighting schemes such as those based on variance assume independence of observations within individuals at each data point.

(iii) Weighting schemes require replicates of an experimental design. Although these are available here, initial kinetic studies on new drugs rarely provide such data.

The data from each patient were run as a triexponential fit using the formula:

plasma concentration =

$$A\exp-\alpha\, t+B\exp-\beta\, t+C\exp-\gamma\, t$$

Kinetic parameters were then calculated (Wagner, 1976).

The statistical significance of differences between demographic parameters and between plasma concentrations was used to assess the overall difference between the plasma concentrations of the two groups.

*Calculations from literature data*

The clearance values from the literature (Inturrisi and Verebely, 1972a,b; Kreek, 1973; Verebely et al., 1975; Holmstrand, Anggard and Gunne, 1978) (table IV) were obtained (Wagner, 1976) using the formulae:

Clearance at steady state (ml min$^{-1}$)

$$=\frac{\text{dose per min}}{\text{steady state plasma concn}}$$

Dose per minute was calculated from the daily dose of each patient. Either the steady state plasma concentration was given (Verebely et al., 1975) or the pre-dose value was used (Inturrisi and Verebely, 1972a,b; Kreek, 1973; Holmstrand, Anggard and Gunne, 1978).

## RESULTS

The patient data are summarized in table I. The significant differences in $Pa_{CO_2}$ were a result of the spontaneous ventilation after operation in group P compared with the intraoperative controlled ventilation in group I. The difference in arterial pressure between the two groups may be ascribed to a continuing cardiovascular effect of the extradural in group P which decreased over the 3-h pharmacokinetic study period. There were no other statistically significant differences.

The average plasma concentrations for the two groups are presented in table II. The concentration

TABLE I. *Demographic data (mean ± SEM). †P < 0.01, paired* t *test; ***P < 0.001, unpaired* t *test*

| | Group I | Group P |
|---|---|---|
| Number of patients | 14 | 12 |
| Age (yr) | 62.9 ± 2.6 | 64.2 ± 2.0 |
| Weight (kg) | 71.7 ± 3.4 | 73.1 ± 4.0 |
| Height (cm) | 169.3 ± 3.6 | 168.5 ± 2.4 |
| Dose (mg kg$^{-1}$) | 0.144 ± 0.007 | 0.142 ± 0.009 |
| Surface area (m$^2$) | 1.76 ± 0.05 | 1.81 ± 0.04 |
| Sex ratio | 8M : 6F | 5M 7F |
| Core temperature (°C) | | |
| 30 min after drug | 35.2 ± 0.15 | 35.3 ± 0.24 |
| 150 min after drug | 35.2 ± 0.18 | 35.6 ± 0.16 |
| Mean AP (mm Hg) | | |
| 30 min after drug | 75.8 ± 8.4 | 69.1 ± 5.5† |
| 150 min after drug | 84.8 ± 4.8 | 88.1 ± 4.2† |
| $Pa_{CO_2}$ (kPa) | | |
| 30 min after drug | 5.10 ± 0.2 | 6.97 ± 0.25*** |
| Surgery time (min) | 86 ± 8 | 85 ± 8 |
| Blood loss (ml) | 611 ± 46 | 411 ± 90 |

TABLE II. *Plasma concentrations of methadone base (ng ml$^{-1}$) (mean ± SEM).* n = *14 for group I, except ‡10 and †8;* n = *12 for group P, except §11.* **P *< 0.05, Student's* t *test*

| Time (min) | Group I | Group P |
|---|---|---|
| 2 | 226.4 ± 13.1 | 241.7 ± 25.6 |
| 5 | 123.9 ± 8.2 | 146.0 ± 16.7§ |
| 7.5 | 82.9 ± 6.6 | 85.4 ± 7.1 |
| 10 | 69.7 ± 4.0 | 72.7 ± 5.3 |
| 20 | 54.6 ± 4.1 | 59.3 ± 4.7 |
| 30 | 47.3 ± 3.6 | 54.1 ± 4.3 |
| 40 | 40.9 ± 2.8 | 48.9 ± 4.1 |
| 60 | 33.8 ± 2.5 | 41.3 ± 3.7 |
| 80 | 32.6 ± 2.6 | 37.8 ± 2.9 |
| 100 | 29.7 ± 2.5 | 37.5 ± 2.1** |
| 120 | 29.6 ± 2.6 | 34.8 ± 2.6 |
| 150 | 28.0 ± 2.1 | 33.7 ± 2.7 |
| 180 | 28.1 ± 3.2 | 33.0 ± 3.0 |
| 210 | 25.0 ± 2.3‡ | |
| 240 | 24.2 ± 2.9† | |
| 270 | 20.6 ± 2.2† | |
| 300 | 21.5 ± 2.6† | |
| 330 | 21.2 ± 2.2† | |
| 360 | 16.1 ± 1.5† | |

at 100 min was significantly greater in group P than in group I ($P < 0.05$). All the group P values were greater than those for group I and overall this difference was statistically significant ($n = 13$, $P < 0.002$, sign test).

The kinetic parameters derived from triexponential fits (table III), showed $A$, $T_{\frac{1}{2}}^{\alpha}$, $\beta$ and $T_{\frac{1}{2}}^{\beta}$ values which were similar in both groups. The initial distribution volumes ($V_P$) were also very similar at about 25 litre. The plasma clearances at about 150 ml min$^{-1}$ were not significantly different for 3- or 6-h data and were comparable to values obtained from the chronic studies in the literature (table IV). However, the terminal half-lives were very long and showed a wide range and were very different from chronic dosing studies.

## DISCUSSION

Plasma concentrations of methadone decreased rapidly from their initial values, as expected for this very lipophilic drug. Average plasma concentrations for the intraoperative (I) group were consistently lower than those for the postoperative (P) group; this trend was statistically significant using a sign test. The latter group showed a significant increase in mean arterial pressure over the study period and this suggests a cardiovascular basis for this differ-

TABLE III. *Kinetic parameters (individual patient plasma concentrations) (mean ± SEM). The kinetic parameters were derived from the NONLIN analysis using the formula: plasma concentration =* $A \exp - \alpha t + B \exp - \beta t + C \exp - \gamma t$ *for triexponential fits.* $V_P$ *is the initial volume of distribution*

| | Group I | Group P |
|---|---|---|
| Number of patients | 14 | 12 |
| Number of data points | 19 | 13 |
| $A$ (ng ml$^{-1}$) | 377.4 ± 47.5 | 481.7 ± 168.9 |
| $B$ (ng ml$^{-1}$) | 51.0 ± 10.1 | 59.6 ± 19.6 |
| $C$ (ng ml$^{-1}$) | 30.0 ± 3.7 | 36.2 ± 6.1 |
| $T_{\frac{1}{2}}^{\alpha}$ (min) | 2.06 ± 0.3 | 2.13 ± 0.2 |
| $T_{\frac{1}{2}}^{\beta}$ (min) | 27.3 ± 3.7 | 31.8 ± 7.1 |
| $T_{\frac{1}{2}}^{\gamma}$ (min) | 84096 ± 47831 | 81717 ± 37876 |
| (range) | (165 – 647801) | (134 – 402993) |
| Clearance (ml min$^{-1}$) | 162.7 ± 49.3 | 149.4 ± 61.8 |
| $V_P$ (litre) | 23.0 ± 2.4 | 25.5 ± 3.8 |

TABLE IV. *Half-life and clearance values from the literature compared with present acute study (footnotes (8a) and (8b)). *Calculated as described in the text. GLC = gas–liquid chromatography; MS = mass spectrometry; RIA = radioimmunoassay*

| Terminal $T_{\frac{1}{2}}$ (h) | Clearance (ml min$^{-1}$) | No. of patients | Footnote |
|---|---|---|---|
| 14.8 ± 1.6 | | 5 | (1) Inturrisi and Verebely (1972a) |
| 22.2 ± 2.0 | 147.8 ± 8.9* | 12 | (2) Verebely and others (1975) |
| ~24 | ~140 | 9 | (3) Dole and Kreek (1973) |
| | 121.0 ± 14.8* | 9 | (4) Kreek (1973) |
| 25.4 ± 6.0 | 232.7 ± 70.1* | 5 | (5) Inturrisi and Verebely (1972b) |
| | 254.0 ± 31.8* | 21 | (6) Holmstrand, Anggard and Gunne (1978) |
| 21.6 ± 0.9 | | 5 | (7a) Anggard and others (1979) |
| 52.4 ± 9.1 | | 5 | (7b) Anggard and others (1979) |
| 24.1 ± 1.9 | | 7 | (7c) Anggard and others (1979) |
| 43.1 ± 4.9 | | 7 | (7d) Anggard and others (1979) |
| 1362 ± 631 | 149.4 ± 61.8 | 12 | (8a) |
| 1402 ± 797 | 162.7 ± 49.3 | 14 | (8b) |

FOOTNOTES

(1) Acute, 15 mg oral, GLC
(2) Chronic, 40 or 80 mg oral/24 h, GLC, average plasma concn
(3) Chronic, 100 mg oral/24 h, GLC and isotope dilution
(4) Chronic, 100 mg oral/24 h, GLC and isotope dilution, pre-dose concn
(5) Chronic, 100 or 120 mg oral/24 h, GLC, pre-dose concn
(6) Chronic, 40–85 (usually 60) mg oral/24 h, GLC+MS, pre-dose concn
(7) Chronic, 54–90 mg/24 h, MS
  a = oral, deuterium-labelled isotope
  b = oral, unlabelled
  c = i.v., deuterium-labelled isotope
  d = i.v., unlabelled
(8) Acute, 10 mg i.v., RIA
  a = triexponential fit to individual 3-h data group P
  b = triexponential fit to individual 6-h data group I

ence in methadone concentrations. Vasodilatation produced in the lower extremities by extradural analgesia is compensated by vasoconstriction in the trunk and upper limbs. The effects of extradural blockade used as intraoperative analgesia in group P may not have abated completely, so that the restricted distribution of peripheral blood flow may still have been present at the start of the drug study. Increased plasma drug concentrations would result.

Non-linear regression analysis showed that reproducible values for exponential fits could be obtained for the early phase of the i.v. decay curve. $A$ and $T_{\frac{1}{2}}^{\alpha}$ were much the same for both 3- and 6-h data with a triexponential fit. This indicates that confidence may be placed in these values. Similarly, reliable values for $B$ and $T_{\frac{1}{2}}^{\beta}$ could be obtained. For individuals in both groups a triexponential fit produced a very wide range of terminal half-lives, most of which were biologically unlikely and which did not agree with the values obtained in chronic studies (table IV). A warning of incorrect terminal half-life values is given by wide dispersion measures, indicating little confidence in the estimate.

The conclusions for the estimation of terminal half-life to be drawn from this are that longer duration data (for example 6 rather than 3 h) will not necessarily lead to better estimates of an unknown terminal half-life if this is very long and still well outside the time span of the observations, and that dispersive measures are an invaluable guide to the reliability of the estimates and the confidence which may be placed in them.

The estimation of clearance from the acute data reinforces these points. The clearance values for both 3- and 6-h experiments agreed with chronic studies (tables III, IV). This is despite the unrealistically long terminal half-life produced by these fits. The internal adjustments made by non-linear regression in fitting the data to a theoretical curve are self-compensating; the long $T_{\frac{1}{2}}^{\gamma}$ generates a smaller $C$ value. The contribution to the AUC from this component will now assume the appropriate proportion.

Methadone is a particularly extreme test for estimation of kinetic parameters from an acute i.v. study of limited duration because of its very long terminal half-life. The application of the concepts discussed above is illustrated by consideration of buprenorphine kinetics in a similar group of patients (Bullingham et al., 1980). In that study triexponential fits to 3-h data on 10 patients gave a terminal half-life of 185 ± 35 min (mean ± SEM). Unlike the present study, the low dispersion associated with this value gave some confidence that it was appropriate, although the mean was the same as the study duration. A subsequent 13-h study (Bullingham et al., 1982) only increased the terminal half-life to 311 ± 33 min (mean ± SEM, $n = 5$).

Acute kinetic studies of drugs with long or unknown terminal half-lives can be expected to give reliable estimates of clearance using triexponential fits to short duration data from individual patients, but terminal half-life estimates must always be validated by long duration acute or chronic studies.

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## REFERENCES

Anggard, E., Nilsson, M., Holmstrand, J., and Gunne, L.-M. (1979). Pharmacokinetics of methadone during maintenance therapy: Pulse labelling with deuterated methadone in the steady state. *Eur. J. Clin. Pharmacol.*, **16**, 53.

Bullingham, R. E. S., McQuay, H. J., Moore, R. A., and Bennett, M. R. D. (1980). Buprenorphine kinetics. *Clin. Pharmacol. Ther.*, **28**, 667.

—— —— Porter, E. J. B., Allen, M. C., and Moore, R. A. (1982). Sublingual buprenorphine used postoperatively: ten hour plasma drug concentration analysis. *Br. J. Clin. Pharmacol.*, (in press).

Dole, V. P., and Kreek, M. J. (1973). Methadone plasma level: sustained by a reservoir of drug in the tissue. *Proc. Natl. Acad. Sci. USA*, **70**, 10.

Holmstrand, J., Anggard, E., and Gunne, M.-L. (1978). Methadone maintenance: plasma levels and therapeutic outcome. *Clin. Pharmacol. Ther.*, **23**, 175.

Inturrisi, C. E., and Verebely, K. (1972a). Disposition of methadone in man after a single oral dose. *Clin. Pharmacol. Ther.*, **13**, 923.

—— —— (1972b). The levels of methadone in the plasma in methadone maintenance. *Clin. Pharmacol. Ther.*, **13**, 633.

Kreek, M. J. (1973). Plasma and urine levels of methadone. *N.Y. State J. Med.*, **73**, 2773.

Metzler, C. M., Elfring, G. L., and McEwen, A. J. (1974). A package of computer programs for pharmacokinetic modelling. *Biometrics*, **5**, 562.

Verebely, K., Volavka, J., Mule, S., and Resnick, R. (1975). Methadone in man: pharmacokinetic and excretion studies in acute and chronic treatment. *Clin. Pharmacol. Ther.*, **18**, 180.

Wagner, J. G. (1976). Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. *J. Pharmacokin. Biopharm.*, **4**, 443.

## PHARMACOCINETIQUE DE LA METHADONE INTRAVEINEUSE DE FACON AIGUE CHEZ L'HOMME: COMPARAISON AVEC DES ETUDES CHRONIQUES

### RESUME

Vingt six patients ont reçu 10 mg de méthadone i.v. pour obtenir une pharmacocinétique aiguë chez l'homme. Les concentrations plasmatiques de méthadone ont été mesurées par dosage radioimmunologique sur des études séparées à 3 et 6 h. Les paramètres cinétiques dérivés d'une analyse non linéaire tri-exponentielle ont montré ques les $T_{\frac{1}{2}}^{\alpha}$ et $T_{\frac{1}{2}}^{\beta}$ étaient respectivement de 2 et 30 min. Il n'a pas été possible d'obtenir une estimation fiable de $T_{\frac{1}{2}}^{\gamma}$. La clairance a été estimée à 149 ± 62 et 163 ± 49 ml $min^{-1}$ respectivement pour les études à 3 et 6 h. Ces valeurs ont été comparées avec celles déjà publiées sur l'administration chronique. Les difficultés de la détermination précise de la dernière demi-vie et des valeurs de la clairance pur les études de courte durée sont évoquées. Ces diffultés sont accrues par la longue demi-vie finale de la méthadone. On peut faire dériver des estimations correctes de la clairance à partir d'études de brève durée à condition d'utiliser la moyenne des concordances tri-exponentielles aux données individuelles du patient, même lorsque le recueil des données n'excède pas 3 h. Comme on pouvait s'y attendre, aucune analyse n'a permis d'obtenir des valeurs convenables de la demi-vie terminale de cet agent.

## DIE AKUTE KINETIK VON METHADON I.V. BEIM MENSCHEN: BEZIEHUNG ZU LANGZEITUNTERSUCHUNGEN

### ZUSAMMENFASSUNG

Sechsundzwanzig Patienten erhielten 10 mg Methadon i.v. zur Erforschung der akuten Kinetik am Menschen. Die Plasmakonzentrationen von den Untersuchungen nach 3 und 6 h wurden mit dem Radioimmunassay bestimmt. Die kinetischen Parameter, die von der triexponentialen NONLIN Analyse abgeleitet wurden, zeigten, daß die $T_{\frac{1}{2}}^{\alpha}$ und $T_{\frac{1}{2}}^{\beta}$ 2 und 30 Minuten in obiger Reihenfolge betrugen; von $T_{\frac{1}{2}}^{\gamma}$ konnte keine verläßliche Bestimmung erhalten werden. Die Clearance wurde als 149 ± 62 uns 163 ± 49 ml in den 3 h- und 6 h-Untersuchungen bestimmt. Diese Werte wurden mit den über Langzeitgabe veröffentlichten verglichen. Es werden die Schwierigkeiten, die mit der genauen endgültigen Bestimmung der Halbwertszeit und der Clearance-Werte in Studien von kurzer Dauer verbunden sind, diskutiert. Diese Schwierigkeiten werden durch die lange endgültige Halbwertszeit von Methadon noch verstärkt. Angemessene Bestimmungen der Clearance mögen von einer akuten kurzdauernden Untersuchung gewonnen werden, vorausgesetzt, daß der zu den individuellen Patientendaten passende triexponentielle Durchschnittswert benutzt wird, sogar wenn die Daten sich nur über 3 h erstrecken. Wie vorweggenommen werden mag, ergab keine Untersuchung angemessene Werte für die endgültige Halbwertszeit dieser Substanz.

## ASPECTOS CINETICOS AGUDOS DE LA ADMINISTRACION INTRAVENOSA DE METADONA EN EL HOMBRE: RELACION CON LOS ESTUDIOS DE ADMINISTRACION CRONICA

### SUMARIO

Se administraron intravenosamente 10 mg de metadona a 26 pacientes para obtener características cinéticas intensas en el ser humano. Se midieron mediante pruebas radioinmunes las concentraciones de metadona en el plasma mediante estudios diferentes a intervalos de 3 y de 6 horas. Los parámetros cinéticos derivados del análisis NONLIN triexponencial mostraron que $T_{\frac{1}{2}}^{\alpha}$ y $T_{\frac{1}{2}}^{\beta}$ fueron de 2 y de 30 minutos respectivamente; no pudo obtenerse un valor fiable para $T_{\frac{1}{2}}^{\alpha}$. La eliminación se calculó en 149 ± 62 y 163 ± 49 ml $min^{-1}$ para los estudios de 3 y de 6 horas respectivamente. Estos valores se compararon con los publicados para la administración crónica. Las dificultades existentes en la determinación precisa y definitiva de los valores de eliminación y de vida media obtenidos de los estudios de duración media son discutidos; estas dificultades se acentúan por lo prolongado de la vida media definitiva de la metadona. Los calculos apropiados de la eliminación pueden derivarse de un estudio de duración breve e intensa, en tanto en cuanto se use la media del análisis triexponencial que se adapte al paciente individual, incluso cuando los datos abarquen sólo un periodo de 3 horas. Como podría suponerse, ningún análisis produjo los valores apropiados de vida media definitiva correspondientes a esta droga.

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# EFFICACY OF THE LARYNGEAL REFLEX DURING OXYGEN–NITROUS OXIDE SEDATION (RELATIVE ANALGESIA)

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SUMMARY

The efficacy of the laryngeal reflex during dental treatment in two groups of children was tested using propyliodone 10 ml. In 25 children not specially afraid of dental treatment there was no aspiration of radiopaque dye into the larynx or chest. A similar group of 25 anxious children treated using oxygen–nitrous oxide sedation (relative analgesia) were examined in the same way; there was no aspiration of radiopaque dye.

The use of oxygen and nitrous oxide mixtures (relative analgesia) in dental practice to achieve sedation and analgesia, frequently supplemented by local analgesia, has led to queries regarding its safety for use by the single operator. There has been concern at possible depression of the laryngeal reflex and aspiration of debris from the oral cavity (Pleasants, 1971).

Cleaton-Jones (1976) reported that during "relative analgesia" (50% nitrous oxide in oxygen) the laryngeal reflex remained functional, there being no aspiration of radiopaque dye in adult volunteers. That experiment, however, was carried out 1800 m above sea level where blood saturation of nitrous oxide would be less than at sea level.

Rubin and others (1977) repeated the experiments at sea level. Adult volunteers received 50% nitrous oxide in oxygen as "relative analgesia". Two of 10 volunteers (20%) aspirated contrast medium (Dionosil) to the lungs. It was concluded that the inhalation of 50% nitrous oxide in oxygen differs little from other commonly used anaesthetic techniques with respect to suppression of pharyngeal and laryngeal reflexes (Rubin et al., 1977).

The above studies, whilst showing changes under carefully controlled conditions, are sufficiently different from the circumstances prevailing during clinical practice to justify a study in patients undergoing dental treatment. There are two important differences between "experimental" and "clinical" conditions. First, in the clinical technique of relative analgesia it is considered important to determine the concentration of nitrous oxide in oxygen most suited to each patient by careful titration (Roberts, 1979). This optimum level of sedation is achieved and maintained by assessing the patient's general demeanour, level of consciousness and the ability to maintain an open mouth and verbal contact (Langa, 1976).

Second, it is believed by many clinicians that the response of frightened patients undergoing dental treatment is likely to be different from that of calm volunteers.

It has been shown in adult volunteers that heart rate, arterial pressure, and respiratory rate increased during the administration of oxygen in nitrous oxide (Everett and Allan, 1971). Similar assessments in anxious children showed a slight decrease in arterial pressure, heart rate, and respiratory rate during dental treatment involving local anaesthetic injections and use of the drill (Roberts et al., 1979, 1982).

We have conducted a further assessment of laryngeal competence in anxious and non-anxious children undergoing dental treatment.

## PATIENTS AND METHODS

The study was approved by the ethics committee of the Royal Dental Hospital. Anxious patients referred to the Children's Department were assessed and those requiring oxygen and nitrous oxide sedation were included in the experimental group. The age range of the children was 4–18 yr, and they were matched in the groups for age, sex and the dental treatment required. No child selected had any coexistent medical problems. Consent was obtained from the parents and agreement obtained from the child.

The induction procedure was as follows (Roberts,

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1979). The mixture dial was set to 100% oxygen and the patient settled in the dental chair. The nasal mask was positioned and the patient encouraged to breathe gently through the nose. The flow of oxygen was increased until it matched the patient's tidal volume. At this point the patient was reassured and advised of the sensations likely to be experienced and the mixture dial turned to 10% nitrous oxide and held there for 60 s. Reassurance and encouragement was continued throughout induction. The mixture dial was then turned to 20% nitrous oxide for a further 60 s and if necessary to 30% nitrous oxide for 60 s more. Above this concentration increments of 5% were sometimes used. Satisfactory sedation was judged by the patient's demeanour, reported symptoms such as tingling, and a willingness to accept the needle and the drill. At the end of treatment we administered 100% oxygen for 2 min.

It is crucial to the success of the technique that the amount of nitrous oxide administered to the patient is assessed by careful titration of the nitrous oxide concentration to the patient's individual needs. Care was taken to obtain close adaptation of the nasal hood to the patient's face. During treatment the back of the mouth was observed to confirm that a posterior oral seal was achieved. Patients who exhibited mouth breathing were not included in the study.

All patients were treated in the supine position. Before the start of drilling a sufficient quantity of propyliodone aqueous B.P. (Dionosil Aqueous, Glaxo Laboratories, Greenford, Midd'x) was deposited onto the tongue until the patient swallowed the dye. This was repeated halfway through the operative procedure, and again at the end of dental treatment. The total amount of dye swallowed was in excess of 10 ml. In patients receiving oxygen and nitrous oxide sedation recovery was not started until the third increment of propyliodone had been swallowed. During dental treatment oral suction was carried out only to remove water and saliva. No suction was present when the propyliodone bolus was being placed on the tongue.

Immediately after treatment was completed we obtained a lateral x-ray view of the larynx and throat. The x-ray exposure factors, 7.5 mAs 60 kV, produced a film which showed the soft tissues of the larynx and pharynx (fig. 1). The patient then attended the Radiology Department when a postero-anterior view of the chest was taken (fig. 2). To minimize radiation dose a high speed screen-film combination was used in the radiography of both the neck and chest.

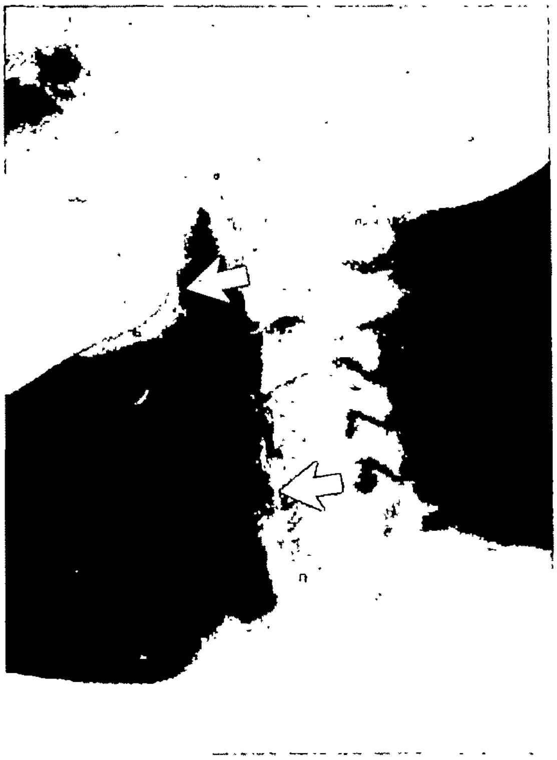

FIG 1. Lateral view of larynx immediately following dental treatment and sedation with 60% nitrous oxide in oxygen. The radiopaque medium coats the posterior third of the tongue and the posterior wall of the oesophagus (arrowed) but is absent from the laryngeal cavity and trachea.

A follow-up questionnaire designed to determine the occurrence of complications after operation, particularly respiratory problems, was returned to one of the investigators. The radiographs were examined by one of us (BKW) who was unaware of the treatment group.

Details of patient's age, sex, treatment time and amount of treatment carried out were recorded for each patient.

## RESULTS

Fifty children aged 4–18 yr were studied, 25 unsedated and 25 sedated with nitrous oxide. These two groups were similar as regards average age, (13 yr 2 months unsedated; 12 yr 9 months sedated). In each group there were 13 males. The amount of treatment, limited to simple fillings, was similar, being 2.52 relative value units for the unsedated and 2.60 relative value units for the sedated, as was the

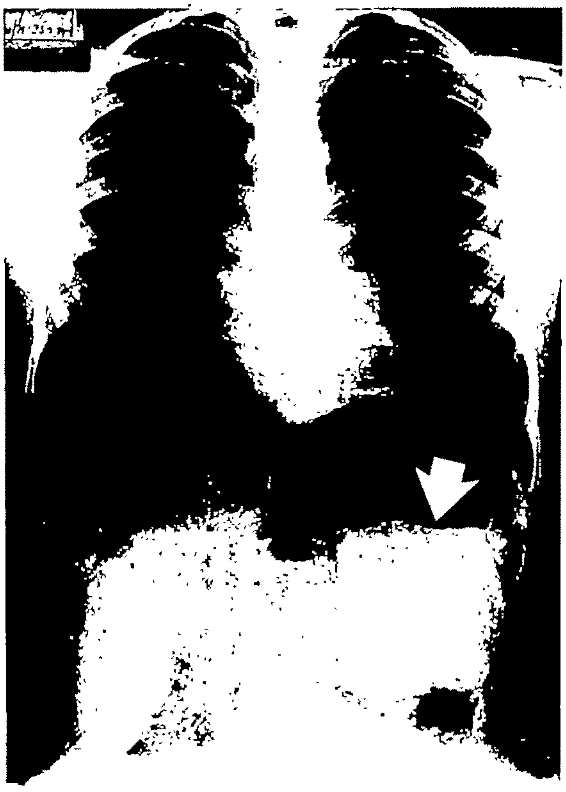

FIG. 2. Postero-anterior view of chest showing radiopaque medium absent from chest, but in the stomach (arrowed). Same patient as figure 1.

treatment time—21 and 20 min respectively.

The sedated group received treatment using concentrations of nitrous oxide which varied from 20% to 65% (table I).

TABLE I. *Concentrations of nitrous oxide used in the experimental group*

| Nitrous oxide (%) | No. of patients |
|---|---|
| 20–24 | 4 |
| 25–29 | 7 |
| 30–34 | 4 |
| 35–39 | 4 |
| 40–44 | 3 |
| 45–49 | 1 |
| 50–54 | — |
| 55–59 | — |
| 60–64 | 2 |

The questionnaire revealed that, in the days and weeks following treatment, there was no apparent increase in respiratory problems or general illness.

## DISCUSSION

The results demonstrate that anxious children receiving dental treatment with nitrous oxide sedation and non-anxious children receiving dental treatment with local anaesthesia do not inhale propyliodone during dental treatment.

The use of propyliodone deposited on the posterior third of the tongue has been used frequently as a test of laryngeal incompetence (Tomlin, Howarth and Robinson, 1968; Wise et al., 1969; Healey, Robinson and Vickers, 1970; Taylor and Towey, 1971; Cleaton-Jones, 1976; Allen, Ricks and Jogensen, 1977; Rubin et al., 1977). All of the above studies have been carried out on adults in whom it has been shown that 10 ml of propyliodone is needed as a single bolus to avoid false negative results (Taylor, Towey and Rappaport, 1972). Examination of these papers reveals a number of methodological differences, some authors placing a single bolus on the dorsal third of the tongue in anaesthetized patients and allowing it to trickle down into the pharynx and on into the larynx (Taylor and Towey, 1971).

In patients sedated with i.v. diazepam a single bolus of propyliodone was placed on the tongue and each patient instructed to swallow (Healy, Robinson and Vickers, 1970). Volunteers sedated with 50% nitrous oxide in oxygen had 10 ml of propyliodone deposited onto the dorsal third of the tongue as a single bolus and were instructed to swallow (Cleaton-Jones, 1976). In the study of Rubin and colleagues (1977) a total of 15 ml of propyliodone was placed on the back of the tongue over a period of 2 min and swallowed by the subjects.

It is clear from the work of Taylor, Towey and Rappaport (1972) that sufficient volume of propyliodone must be used to avoid false negative results. For adults this volume appears to be 10 ml in a single bolus. In the preliminary stages of the present study it was apparent that a single bolus of 10 ml was too large for many of our patients as swallowing was initiated when the bolus reached a critical size for each patient. For this reason the total amount of dye for each patient varied slightly as different children were obliged to swallow at differing times. All patients swallowed at least 10 ml divided into three separate aliquots, some in excess of this total volume. From a practical point of view it is important that the volume of propyliodone is sufficient to avoid a false negative. In the patients under study the laryngeal reflex was challenged three times in each patient with a volume of 3.3 ml or more. Whilst this volume differs from the 10 ml used in adults, it is assumed that for children a reduced volume would be needed to challenge the laryngeal reflex effectively. From our attempts to place a bolus on the dorsal third of the tongue it was clear that the response—the first stage of swallowing—limited the size of each bolus. For this reason a smaller bolus than previously reported (Taylor, Towey and Rappaport, 1972) was used. From a practical point of view the crucial factor would appear to be that the largest bolus tolerated by the patient would be a sufficient challenge to the laryngeal reflexes.

Previous work showed that the laryngeal reflex was not depressed below a critical level in student volunteers undergoing simulated dental procedures (Cleaton-Jones, 1976). This was challenged by Rubin and others (1977) because Cleaton-Jones' work was carried out at 1700 m above sea level and therefore the degree of saturation would be only 80% of that at sea level. Rubin and others (1977) showed that experimental "relative analgesia" using a fixed concentration of 50% nitrous oxide in oxygen resulted in two of 10 volunteers inhaling propyliodone.

Whilst the use of volunteer subjects under carefully controlled conditions has an important role to play in the preliminary evaluation of techniques, and provides a useful means of carrying out a study simulating the conditions prevailing during clinical practice, such laboratory studies can never be a complete substitute for properly designed clinical studies.

The present study has extended the work of Cleaton-Jones (1976) and Rubin and others (1977) by comparing the efficacy of the laryngeal reflex in sedated and non-sedated patients receiving dental treatment.

The unique features are: the use of anxious patients undergoing dental treatment using nitrous oxide sedation with or without local analgesia; the provision of a level of sedation appropriate to the needs of each patient; the comparison of anxious patients receiving nitrous oxide sedation with non-anxious patients receiving local anaesthesia; the use of a lateral view of the larynx in an attempt to detect laryngeal soiling as distinct from bronchial soiling.

From the evidence presented we conclude that the nitrous oxide sedation (relative analgesia) did not put our patients at risk from depression of the laryngeal reflex.

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## REFERENCES

Allen, G. D., Ricks, C. S., and Jorgensen, N. B. (1977). The efficacy of the laryngeal reflex in conscious sedation. *J. Am. Dent. Assoc.*, 94, 901.

Cleaton-Jones, P. (1976). The laryngeal closure reflex and nitrous oxide: oxygen analgesia. *Anesthesiology*, 45, 569.

Everett, G. B., and Allen, G. D. (1971). Simultaneous evaluation of cardiorespiratory and analgesic effects of nitrous oxide: oxygen inhalation analgesia. *J. Am. Dent. Res.*, 83, 120.

Healy, T. E. J., Robinson, J. S., and Vickers, M. D. (1970). Physiological responses to intravenous diazepam as a sedative for conservative dentistry. *Br. Med. J.*, 3, 10.

Langa, H. (1976). *Relative Analgesia*. London: Saunders.

Pleasants, J. (1971). The case against relative analgesia. *Dent. Clin. N. Am.*, 15, 839.

Roberts, G. J. (1979). Relative analgesia—an introduction. *Dent. Update*, 6, 271.

——Gibson, A., Porter, J., and DeZoysa, S. (1979). Relative analgesia: an evaluation of the efficacy and safety. *Br. Dent. J.*, 146, 177.

————————(1982). Physiological changes during relative analgesia—a clinical study. *J. Dent.*, 10, 55.

Rubin, J., Brock-Utne, J. G., Greenberg, M., Bortz, J., and Downing, J. W. (1977). Laryngeal incompetence during experimental "relative analgesia" using 50% nitrous oxide in oxygen. *Br. J. Anaesth.*, 49, 1005.

Taylor, P. A., and Towey, R. M. (1971). Depression of laryngeal reflexes during ketamine anaesthesia. *Br. Med. J.*, 2, 688.

————Rappaport, A. S. (1972). Further work on the depression of laryngeal reflexes during ketamine anaesthesia using a standard challenge technique. *Br. J. Anaesth.*, 44, 1163.

Tomlin, P. J., Howarth, F. H., and Robinson, J. S. (1968). Postoperative atelectasis and laryngeal competence. *Lancet*, 1, 1404.

Wise, C. C., Robinson, J. S., Heath, M. J., and Tomlin, P. J. (1969). Physiological responses to intermittent methohexitone for conservative dentistry. *Br. Med. J.*, 2, 540.

## EFFICACITE DU REFLEXE LARYNGE AU COURS DE LA SEDATION PAR LE PROTOXYDE D'AZOTE DANS L'OXYGENE (ANALGESIE RELATIVE)

### RESUME

On a testé l'efficacité du réflexe laryngé au cours de soins dentaires dans deux groupes d'enfants, en utilisant de la propyléodone 10 ml. Chez 25 enfants qui n'étaient pas particulièrement effrayés par les soins dentaires, il n'y avait pas d'inhalation de la substance radio-opaque dans le larynx ou le thorax. Un groupe comparable de 25 enfants anxieux, traités par une sédation au protoxyde d'azote dans l'oxygène (analgésie relative), a été examiné de la même façon. Il n'y a pas eu d'inhalation de colorant radio-opaque.

## STÄRKE DES KEHLKOPFREFLEXES UNTER SEDIERUNG MIT LACHGAS/SAUERSTAFF (RELATIVE ANALGESIE)

### ZUSAMMENFASSUNG

Die Stärke des Kehlkopfreflexes während zahnärztlicher Behandlung bei Verwendung von Propyliodon 10 ml wurde in zwei Gruppen von Kindern untersucht. Bei 25 Kindern, die keine besondere Angst vor Zahnbehandlung hatten, gab es keine Aspiration von Röntgenkontrastmittel in den Kehlkopf oder die Lunge. Eine ähnliche Gruppe von 25 ängstlichen Kindern, die mit Lachgas/Sauerstoff sediert waren (relative Analgesie), wurden in der selben Weise untersucht. Es fand keine Aspiration von Röntgenkontrastmittel statt.

## EFICACIA DEL REFLEJO LARÍNGEO DURANTE LA SEDACIÓN POR ÓXIDO NITROSO-OXÍGENO (ANALGESIA RELATIVA)

### SUMARIO

Se llevaron a cabo ensayos respecto de la eficacia del reflejo laríngeo durante el tratamiento dentario en dos grupos de niños al usar 10 ml de propiliodona. En 25 niños que no tenían miedo particular al tratamiento dentario, no hubo aspiración de la tintura radio-ópaca en la laringe o el pecho. Un grupo similar de 25 niños ansiosos tratados con sedación por óxido nitroso-oxígeno (analgesia relativa) fueron examinados del mismo modo; no hubo aspiración alguna de la tintura radio-ópaca.

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# A MATCHED COMPARISON OF FOUR SUXAMETHONIUM ADMINISTRATION TECHNIQUES IN PATIENTS WITH STRABISMUS

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## SUMMARY

Four methods of administering suxamethonium were compared in patients undergoing surgery for strabismus who were matched for sex, age, weight and height. Pre-treatment with tubocurarine afforded the best control of suxamethonium-induced sequelae. Serum potassium remained within normal limits suggesting that individuals with strabismus behave differently from those free of this defect.

As advocated by Mayrhofer (1959), the administration of tubocurarine 0.05 mg $kg^{-1}$, if given 3 min (Takki, Kauste and Kjellberg, 1972) before suxamethonium 1.5 mg $kg^{-1}$ (Cullen, 1971) is capable of controlling the fasciculations of the depolarizing relaxant and affords satisfactory intubating conditions. The search continues for alternative methods to reduce the suxamethonium-induced sequelae. Diazepam has long been thought effective for this (Tonsa, 1966; Parada, 1968; di Giacomo, Beyer and Müller, 1970) but a more recent study reporting its benefits (Fahmy, Malek and Lappas, 1979) has been rebutted (Erkola, Salmenperä and Tammisto, 1980). Other compounds such as ascorbic acid (Gupte and Savant, 1971) and dantrolene (Collier, 1979; Plötz, Braun and Stallenberger, 1981) have been described as being, respectively, of no value (Wood et al., 1977) or unsuitable (Agoston, 1980).

Foldes (1973 and personal communication) and Baraka (1977) advocate "special handling" of suxamethonium for controlling the fasciculations so inherent with the i.v. injection. However, reports are conflicting (Mitchell and Brooks, 1978; Restelli et al., 1980; Wilson and Dundee, 1980).

The modification of Mayrhofer's technique mentioned earlier is our standard procedure when suxamethonium is given for endotracheal intubation. To determine if the methods of Foldes (1973) and Baraka (1977) would offer any advantages over this method, and using untreated suxamethonium as control, a study was designed involving matched groups of patients undergoing surgical correction for strabismus.

## METHODS

Sixty patients undergoing anaesthesia and surgery for strabismus, of either sex, aged 6–56 yr and in good health were studied in 15 groups, each of four patients, matched for sex, age, weight and height. The limits of matching, except for children and adolescents, were within 15 years of age, 15 kg weight, and 15 cm height. Four methods of suxamethonium (Sx) administration for endotracheal intubation were allotted at random to the four members of each group.

The patients received atropine 0.01 mg $kg^{-1}$ and pethidine 1 mg $kg^{-1}$ i.m. 30–60 min before the start of anaesthesia. In the operating room, e.c.g. (precordial electrodes; lead II) was recorded on to an Elema Mingograph and a sphygmomanometer cuff was placed around the left forearm for arterial pressure measurement. The right cubital vein was cannulated and blood samples taken for serum creatine kinase (CK) and potassium (K) determinations. A buffered 5% glucose solution was connected to the cannula into which all drugs were given. The patients breathed oxygen from a facemask before thiopentone 5 mg $kg^{-1}$ was given over a period of 10 s.

The four i.v. methods of Sx administration, after the loss of verbal response to thiopentone, to enable endotracheal intubation are:

(I) Suxamethonium 1 mg $kg^{-1}$ given in 3 s.
(II) Suxamethonium 0.14 mg $kg^{-1}$ injected and after 45–60 s, Sx 1 mg $kg^{-1}$ administered over a 5-s period.
(III) Suxamethonium 0.6 mg $kg^{-1}$ given over 30 s into the fast running glucose solution. The

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first one-third was injected in 15 s and the second two-thirds in the next 15 s.

(IV) Tubocurarine 0.05 mg $kg^{-1}$ i.v. preceded thiopentone administration by 2.5 min. When 3 min had elapsed from the time of the tubocurarine injection, suxamethonium 1.5 mg $kg^{-1}$ was given within 3 s.

After tracheal intubation the patients breathed, from a non-rebreathing system, nitrous oxide in oxygen (4:2) and 1% halothane. End-tidal carbon dioxide was maintained between 4.5 and 6% and recorded. Increments of pethidine were given i.v. to supplement anaesthesia.

The same two anaesthetists undertook the study, one (PB) being in charge of grading the level of Sx-provoked fasciculations (0 = absent, 1 = mild, 2 = moderate, 3 = severe) and intubating conditions (0 = vocal cords abducted, no movement of diaphragm: 1 = vocal cords abducted, slight diaphragmatic movement: 2 = vocal cords slightly moving, gross movements of diaphragm: 3 = impossible to intubate). The second anaesthetist (UK) gave all the drugs during the study period and took the necessary blood samples. Care was taken that the first anaesthetist did not know what administration technique was used.

Blood was sampled with minimal or no stasis applied and no flushing of the cannula, which had been inserted into the great saphenous vein in the foot. If this cannula became occluded, the vein in the contralateral foot was used. Blood for serum K determination was taken before and at 1, 3, 5, 7, and 10 min after Sx administration and analysed immediately by a flame photometric technique. Blood for serum CK was collected just before anaesthesia, at 24 and 48 h later and stored at −20 °C until measured according to the Recommendations of the Scandinavian Committee on Enzymes (Committee, 1976). The method is sensitive and eliminates the possibility of enzyme inactivation. In the laboratory here, 170 u. $litre^{-1}$ and 220 u. $litre^{-1}$ are the upper normal limits for females and males respectively.

During the 8-month period of investigation, 13 ampoules of suxamethonium used were at random returned to the manufacturer, who determined the activity of the relaxant according to the monograph for Succinylcholine Chloride Injection in the British Pharmacopoeia (BP) (1973).

The Friedman test and Cochran's $Q$ test were used for statistical handling of CK and fasciculation/intubation conditions respectively. These are non-parametric tests taking into account the matching. The former test permits the analysis of data which are not normally distributed. Mean serum K values of the four methods were compared by analysis of variance. Statistical significance was indicated by a probability value $P < 0.05$.

## RESULTS

The efficiency of matching of age, weight and height is shown in table I. Clearly, there are no large differences on average for any of the three variables.

Serum that yielded extraordinarily large CK values was re-examined about 1 week after the first measurements had been made. In all cases the repeat values were less than the first, indicating that CK activity decreased with storage. Where duplication was made, the first values were used for statistical analysis. As the delay in analysing the specimens occurred with similar frequency, it is reasonable to assume that the comparison of CK values is not confounded by this factor. CK concentrations before induction of anaesthesia were similar among the four methods. The mean ranks between the various techniques, that is within times, did not differ significantly (table II). On the other hand, when the mean ranks between times (within techniques) were studied, $P = 0.01, 0.00, 0.06$ and $0.04$ for methods I, II, III and IV respectively. The trends were upward from 0 to 24 h but then diminished from 24 to 48 h.

By examining the standard deviations in table II between the methods one could well consider these clinically important. In this respect, method IV had the least variation and method I the greatest.

Serum K concentrations remained well within normal limits over the 10-min sampling period. As there was no evidence that these values were not normally distributed, an analysis of variance was applied. This was used to reveal if there were method or time effects, or both, and whether these two factors, technique and time, interact. The means and standard deviations of the K values are seen in table III. An increasing trend with time was noted in all four methods, method IV resulting in the least change and that of method I, the greatest. Clinically, however, these alterations cannot be considered significant. Statistically, over all times combined, there were no significant differences between techniques ($F = 0.93$: $P > 0.05$). There were, however, significant differences in the time means for all techniques combined ($F = 2.767$: $0.05 > P > 0.025$). Furthermore, there was no interaction between technique and time ($F = 0.77$:

TABLE I. *Summary of the efficiency of matching*

| | Method of suxamethonium administration | | | |
|---|---|---|---|---|
| | I | II | III | IV |
| Sex (number of males) | 5 | 5 | 5 | 5 |
| Mean age (yr ± SD) | 22.9 ± 10.5 | 23.5 ± 12.0 | 24.4 ± 12.9 | 24.5 ± 13.9 |
| Mean weight (kg ± SD) | 56.9 ± 14.4 | 57.1 ± 19.9 | 56.7 ± 15.3 | 57.3 ± 13.9 |
| Mean height (cm ± SD) | 161 ± 15 | 160 ± 18 | 162 ± 14 | 162 ± 19 |

TABLE II. *Mean CK activity (u. litre$^{-1}$ ± SD). (Note that mean ranks shown can only be compared within a column and not within a row)*

| | Time (h) | | |
|---|---|---|---|
| Method of Sx admin. | 0 | 24 | 48 |
| I | 81.3 ± 40.7 | 413.4 ± 611.1 | 282.5 ± 378.5 |
| Mean rank | 2.40 | 2.87 | 2.83 |
| II | 83.5 ± 39.8 | 306.0 ± 365.8 | 198.3 ± 193.2 |
| Mean rank | 2.63 | 2.47 | 2.40 |
| III | 93.0 ± 46.9 | 216.1 ± 223.0 | 175.2 ± 131.5 |
| Mean rank | 2.83 | 2.57 | 2.73 |
| IV | 75.9 ± 37.7 | 204.1 ± 168.0 | 161.4 ± 131.5 |
| Mean rank | 2.13 | 2.10 | 2.03 |
| Chi square | 2.46 | 2.70 | 3.54 |
| d.f. | 3 | 3 | 3 |
| *P* | 0.30–0.50 | 0.30–0.50 | 0.30–0.50 |

TABLE III. *Mean serum potassium values (mmol litre$^{-1}$ ± SD)*

| | Time (min) | | | | | |
|---|---|---|---|---|---|---|
| Method of Sx admin. | 0 | 1 | 3 | 5 | 7 | 10 |
| I | 4.11<br>±0.35 | 4.11<br>±0.23 | 4.13<br>±0.21 | 4.11<br>±0.23 | 4.15<br>±0.22 | 4.22<br>±0.23 |
| II | 4.08<br>±0.28 | 4.15<br>±0.29 | 4.11<br>±0.26 | 4.12<br>±0.23 | 4.11<br>±0.27 | 4.16<br>±0.23 |
| III | 4.08<br>±0.16 | 4.23<br>±0.23 | 4.12<br>±0.25 | 4.17<br>±0.24 | 4.16<br>±0.19 | 4.21<br>±0.23 |
| IV | 4.20<br>±0.18 | 4.20<br>±0.17 | 4.25<br>±0.18 | 4.22<br>±0.18 | 4.21<br>±0.18 | 4.27<br>±0.22 |

$P > 0.20$). This latter result indicates that there were no significant differences, on average, between techniques at each time and that the overall trend in time means was consistent for each method.

Table IV summarizes the fasciculations and intubating conditions seen in the study. It is obvious that method I produced the greatest and method IV the least amount of fasciculations. As regards intubating conditions, methods I and IV provided the best situation. Statistically, because of the small number of patients in each group, a dichotomous classification, 0 and 1, was used, 1 being indicative of an adverse condition. Table IV shows the frequency (%) of adverse fasciculations and intubating conditions. Application of Cochran's $Q$ test, which takes into account the matching, shows that there are significant differences among the methods used as regards the frequency of adverse fasciculations, largely because of the lower frequency of fasciculations with method IV ($Q = 40.20$; d.f. = 3; $P < 0.001$). However, no significant differences were found in the frequency of adverse intubating conditions between the four techniques.

Methods II and III resulted in slowing of heart rates in 10 and three patients respectively. The decrease in the case of method II ranged from 8 to 50 (mean 26) beat $\text{min}^{-1}$ while in method III the range was 15–63 (mean 36) beat $\text{min}^{-1}$. The slowing of heart rate was noted when comparing the rates immediately before start of anaesthesia with those following suxamethonium, that is just before endotracheal intubation. During this time, the e.c.g. changes that occurred within the methods were: II, junctional wandering pacemaker 2, bigeminy 2; III, junctional wandering pacemaker 1, aberrations 2; IV, junctional wandering pacemaker 2.

The ampoules of suxamethonium analysed contained hydrolysis products well within the limits of the Assay for Succinylcholine Injection in the British Pharmacopoeia. The fasciculations therefore could not have been affected by the relaxant, *per se*.

TABLE IV. *Frequency (%) of adverse (grades 2 and 3) fasciculations and intubating conditions*

| Method of suxamethonium administration | Fasciculations | Intubation |
|---|---|---|
| I | 80.0 | 0.0 |
| II | 53.3 | 20.0 |
| III | 80.0 | 26.7 |
| IV | 13.3 | 6.7 |
| Cochran's $Q$ test | 40.20 | 5.00 |
| d.f. | 3 | 3 |
| $P$ | <0.001 | 0.10–0.20 |

DISCUSSION

The study was limited to patients with strabismus on the basis of a hypothesis originating here which proposes that such persons, because of a defect in their skeletal muscle biochemistry, respond differently to suxamethonium (Tammisto et al., 1970). It is well known that the greater the skeletal muscle trauma, the greater are the concentrations of CK. As surgery for squint would produce limited injury, changes in CK would be more indicative of those evolving from Sx-induced fasciculations and their subsequent "damage" or "strain", or "increased outflux" of the affected muscle part. Matching was done to give a more sensitive statistical comparison of the techniques as it reduced the random variation between groups.

The size of the standard deviations of CK provide valuable information. Method IV gave a more limited range of change than did the others. This correlates well with the level of fasciculations, which were minimal with this method.

The behaviour of serum K is particularly surprising in that, even in method I, the electrolyte remained within normal limits. This finding disagrees with that of Berkebile, Pfaeffle and Smith (1973), who noted a stastistically significant increase after Sx administration in seven patients with squint. Our finding seems to add support to the hypothesis of Tammisto and others (1970).

The most apparent e.c.g. finding was the slowing of heart rate in 10 patients who received suxamethonium according to method II. This technique is one of intermittent administration, the second dose provoking the slowing. Junctional wandering pacemaker seen in all but method I is obviously an escape rhythm resulting from the slowing of the rapid rate. Perhaps the changes in e.c.g. could have been prevented had a potent antimuscarinic drug such as glycopyrrolate been given i.v. just before start of anaesthesia (Cozanitis, Dundee and Khan, 1980).

The results of this investigation suggest that "special handling" of Sx (methods II and III) do not offer any advantages over the injection of tubocurarine $0.05\ \text{mg kg}^{-1}$ 3 min before the administration of Sx $1.5\ \text{mg kg}^{-1}$ for controlling the sequelae of i.v. injected Sx. Failure of serum K to increase in patients with squint after untreated Sx indicates that these individuals should be studied further.

### REFERENCES

Agoston, S. (1980). Dantrolene and suxamethonium. *Anaesthesia*, 35, 1012.

Baraka, A. (1977). Self-taming of succinylcholine-induced fasciculations. *Anesthesiology*, 46, 292.

Berkebile, P.E., Pfaeffle, H.H., and Smith, R.D. (1973). Succinylcholine induced hyperkalaemia in patients with strabismus. *Can. Anaesth. Soc. J.*, 20, 170.

Collier, C.B. (1979). Dantrolene and suxamethonium. *Anaesthesia*, 34, 152.

Committee (1976). The committee on enzymes of the Scandinavian Society for clinical chemistry and clinical physiology: Recommended method for the determination of creatine kinase in blood. *Scand. J. Clin. Lab. Invest.*, 36, 711.

Cozanitis, D.A., Dundee, J.W., and Khan, M.M. (1980). Comparative study of atropine and glycopyrrolate on suxamethonium-induced changes in cardiac rate and rhythm. *Br. J. Anaesth.*, 52, 291.

Cullen, D.J. (1971). The effect of pretreatment with non-depolarizing muscle relaxants on the neuromuscular blocking action of succinylcholine. *Anesthesiology*, 35, 572.

di Giacomo, G., Beyer, A., and Müller, H. (1970). Erfahrungen mit Faustan zur Prophylaxe der Muskelschmerzen nach Succinylcholinanwendung. *Zentralbl. Chir.*, 95, 957.

Erkola, O., Salmenperä, M., and Tammisto, T. (1980). Does diazepam pretreatment prevent succinylcholine-induced fasciculations? A double-blind comparison of diazepam and tubocurarine pretreatments. *Anesth. Analg. (Cleve.)*, 59, 932.

Fahmy, N.R., Malek, N.S., and Lappas, D.G. (1979). Diazepam prevents some adverse effects of succinylcholine. *Clin. Pharmacol. Ther.*, 26, 395.

Foldes, F.F. (1973). Neuroleptanesthesia for general surgery. *Int. Anesthesiol. Clin.*, 11, 1.

Gupte, S.R., and Savant, S.N. (1971). Post suxamethonium pains and vitamin C. *Anaesthesia*, 26, 436.

Mayrhofer, O. (1959). Die Wirksamkeit von d-Tubocurarin zur Verhutung der Muskelschmerzen nach Succinylcholin. *Anaesthesist*, 8, 313.

Mitchell, L.A., and Brooks, J.L. jr (1978). Succinylcholine pretreatment unsatisfactory. *Anesthesiology*, 48, 297.

Parada, J.F. (1968). Propanidid mit Diazepam zur Einleitung der Procain-bzw. Lachgasnarkose. *Anaesthesist*, 17, 267.

Plötz, J., Braun, J., and Stallenberger, R. (1981). Inhibitorishe Wirkung von Dantrolene auf den Aktivitätsanstieg der Serum-CK nach gemeinsamer Anwendung von Halothan und Succinylcholin beim Menschen. *Anaesthesist*, 30, 338.

Restelli, L., Miriano, F., Pinciroli, D., and Movilia, P. (1980). Les douleurs consécutives à l'administration de suxaméthonium. *Anesth. Analg. Réan.*, 37, 389.

Takki, S., Kauste, A., and Kjellberg, M. (1972). Prevention of suxamethonium-induced fasciculations by prior dose of d-tubocurarine. *Acta Anaesthesiol. Scand.*, 16, 230.

Tammisto, T., Brander, P., Airaksinen, M.M., Tommila, V., and Listola, J. (1970). Strabismus as a possible sign of latent muscular disease predisposing to suxamethonium-induced muscular injury. *Ann. Clin. Res.*, 2, 126.

Tonsa, A. (1966). Prophylaxe des succinylcholibedingten Muskelkaters mit Diazepam. *Anaesthesist*, 15, 363.

Wilson, D.B., and Dundee, J.W. (1980). Failure of divided doses of succinylcholine to reduce the incidence of muscle pains. *Anesthesiology*, 52, 273.

Wood, J.B., Attwood, E.C., Wood, B.M., Dowling, R.M.B., and Bradley, F. (1977). Vitamin C and post-suxamethonium pains. *Anaesthesia*, 32, 21.

## ETUDE COMPARATIVE DE QUATRE TECHNIQUES D'ADMINISTRATION DU SUXAMETHONIUM CHEZ DES PATIENTS SOUFFRANT DE STRABISME

### RESUME

Quatre méthodes d'administration du suxaméthonium ont été comparées chez des patients subissant une chirurgie du strabisme et de sexe, d'âge, de poids et de taille comparables. C'est avec un traitement préalable par la tubocurarine que l'on obtenait la meilleure prévention des séquelles dues au suxaméthonium. La kaliémie restait dans les limites de la normale, ce qui suggère que les individus porteurs d'un strabisme ont un comportement différent de celui des individus normaux.

## EIN PASSENDER VERGLEICH VON VIER VERABREICHUNGSTECHNIKEN VON SUXAMETHONIUM BEI PATIENTEN MIT STRABISMUS

### ZUSAMMENFASSUNG

Vier Verabreichungsformen von Suxamethonium wurden bei Patienten verglichen, die sich einer Strabismus-Operation unterziehen mußten und die in Bezug auf Geschlecht, Alter, Gewicht und Größe vergleichbar waren. Durch Vorbehandlung mit Tubokurarin konnten die auf Suxamethonium folgenden Nebenwirkungen am besten beherrscht werden. Das Serumkalium blieb im Normbereich, was darauf hinweist, daß Individuen mit Strabismus sich hier anders verhalten als jene ohne diesen Defekt.

## UNA COMPARACIÓN CONTRAPUESTA DE CUATRO TÉCNICAS DE ADMINISTRACIÓN DEL SUXAMETONIO EN PACIENTES CON ESTRABISMO

### SUMARIO

Se llevó a cabo una comparación de cuatro métodos de administración del suxametonio en pacientes sometidos a cirujía para estrabismo que tenían la misma edad, el mismo sexo, peso y altura. El pre-tratamiento con tubocurarina permitió el mejor control de las consecuencias inducidas por el suxametonio. El potásio en el suero se mantuvo dentro de límites normales, lo que hace pensar que los individuos afectados por el estrabismo se comportan de manera distinta de los que no padecen de dicho defecto.

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# THE ORIGIN OF INVERTED WAVEFORMS IN THE REFLECTION PLETHYSMOGRAM

J. A. NIJBOER AND J. C. DORLAS

## SUMMARY

In reflection plethysmography at the finger inverted pulsewaves are sometimes observed, especially when, during anaesthesia, arterial pressure is measured in the same arm with an inflatable cuff. The origin of this inversion is investigated in two series of experiments with volunteers. In the first series of experiments the influence of the pressure in the upper arm cuff was investigated and in the second series the influence of the application pressure of the transducer on the finger. It is concluded that inversion of the pulse waves of the plethysmogram is a local phenomenon restricted to the reflection method. It is caused by a relative increase in the optical density of the surrounding tissue in relation to the arterial vessels. In the finger it is brought about by venous engorgement and it is dependent on the applied pressure.

Photoelectric plethysmography is often used during anaesthesia to monitor the peripheral circulation (Otteni, Sauvage and Gauthier-Lafaye, 1969, 1970, 1971; Dorlas, 1974; Johnstone, 1974a, b; Körner, 1974; Sara and Shanks, 1978).

The plethysmogram is most often detected by the reflection method from the distal phalanx of a finger and it is sometimes observed that inverted pulse waves occur. This is a temporary phenomenon which may be seen during anaesthesia when arterial pressure is measured in the same arm with an inflatable cuff (fig. 1). Before and after the pressure measurement the plethysmogram shows the normal waveform. We observed inversions when the reflection plethysmogram was taken from the radial artery and Weinman, Hayat and Raviv (1977) found these inversions at the carotid artery by changing the position of the transducer in relation to the artery.

It is notable that inversions are never seen in the transmission plethysmogram.

The inversions in the reflection plethysmogram during anaesthesia could be reproduced easily after we realized that, besides venous engorgement, the application pressure of the transducer also plays a part. Therefore the importance of these factors for the origin of the inversion phenomenon was investigated in two series of experiments with volunteers.

## METHODS

The experiments were performed on 10 healthy volunteers, eight men and two women, varying in age from 22 to 55 yr. After some preliminary trials the following experimental arrangement proved to be appropriate. The volunteers sat with the measuring arm resting on a soft support with the elbow slightly flexed. The fingers were dependent, about 30 cm below heart level. At the distal phalanx of the index finger, a reflection transducer was fixed with the aid of a small inflatable cuff. At the little finger of the same hand a transmission transducer was fixed. Both transducers (Philips monitoring system type XV 1504/10) function within the infra-red spectrum. A normal inflatable arterial pressure cuff was attached around the upper arm.

In the first series of experiments the influence of the pressure in the upper arm cuff was investigated, while the pressure in the finger cuff was maintained constant at 20 mm Hg to obtain a good attachment of the transducer at the finger.

The upper arm cuff was first inflated, within 5–10 s, until the pulse waves of the plethysmogram had disappeared and then slowly deflated over about 1 min. After the inversion phenomenon was obtained the experiment was repeated twice with an interval of 10–15 min.

In the second series of experiments the influence of the application pressure of the transducer was investigated. The upper arm cuff was first inflated to greater than the systolic arterial pressure and then slowly deflated until the reflection plethysmogram showed clearly recognizable inversions. With the pressure in the upper arm cuff kept constant at this pressure, the pressure in the finger cuff was first increased in 10-mm Hg steps until the pulse waves

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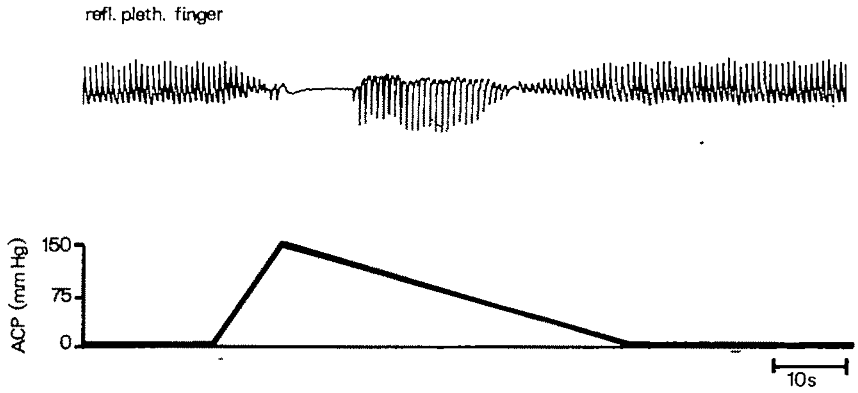

FIG. 1. Inversion of the finger plethysmogram during arterial pressure measurement in the same arm. ACP = arm cuff pressure; refl. pleth. = reflection plethysmogram.

in the plethysmogram had disappeared and subsequently reduced stepwise until the original pressure was reached.

The application pressure of the transmission transducer on the other finger was not changed during these experiments.

The reflection and transmission plethysmograms were simultaneously recorded on a two-channel recorder (Philips AR200). The pressure in the upperarm and finger cuff were read and noted at each alteration.

## RESULTS

In all volunteers, independent of age or sex, the same pattern of results was obtained.

Figure 2 shows a typical example of the results in the first series of experiments. When the pressure in the upper arm cuff decreased to less than the systolic pressure (120 mm Hg) the pulse waves in both plethysmograms returned, but those of the transmission plethysmogram had normal wave forms whereas those of the reflection plethysmogram were inverted. At progressive slow deflation of the upper arm cuff the amplitude of the transmission plethysmogram increased gradually to the original value. The amplitude of the inverted reflection plethysmogram initially increased, but after a stable period it suddenly decreased (at about 45 mm Hg) and became minimal at about 35 mm Hg. Still further reduction of the arm cuff pressure resulted in the return of the normal waveform of the reflection plethysmogram with an increase in amplitude up to the original value.

Figure 3 shows a typical example of the second series of experiments. These started with an inverted reflection plethysmogram brought about by the deflation of the upper arm cuff to about 60 mm Hg. Increasing the pressure in the finger cuff, in steps of 10 mm Hg, caused small increases in amplitude of the inverted reflection plethysmogram, until at about 70 mm Hg the amplitude and the wave form became hardly recognizable. Increasing the pressure in the finger cuff stepwise again produced a return of the normal waveforms. The amplitude first increased, but disappeared when the systolic pressure was reached.

On subsequent stepwise deflation of the finger cuff, the reverse sequence of events occurred, so that at pressure less than about 70 mm Hg the reflection plethysmogram became inverted again and its amplitude declined to its starting value. During these experiments the transmission plethysmogram, taken from the little finger of the same hand, did not change.

## DISCUSSION

In photoelectric plethysmography tissue is illuminated by a small light source. In the tissue the emitted light is partly absorbed and scattered. The remaining part emerges from the tissue and can be detected by a photoelectric cell. The intensity of the detected light shows small changes synchronous with the arterial blood pulsations, giving rise to the plethysmogram. Whether such a small change in detected light, caused by an arterial pulsation, means an increase or decrease in light emerging from the tissue, depends on several optical factors. The absorption coefficient of blood is very high, so

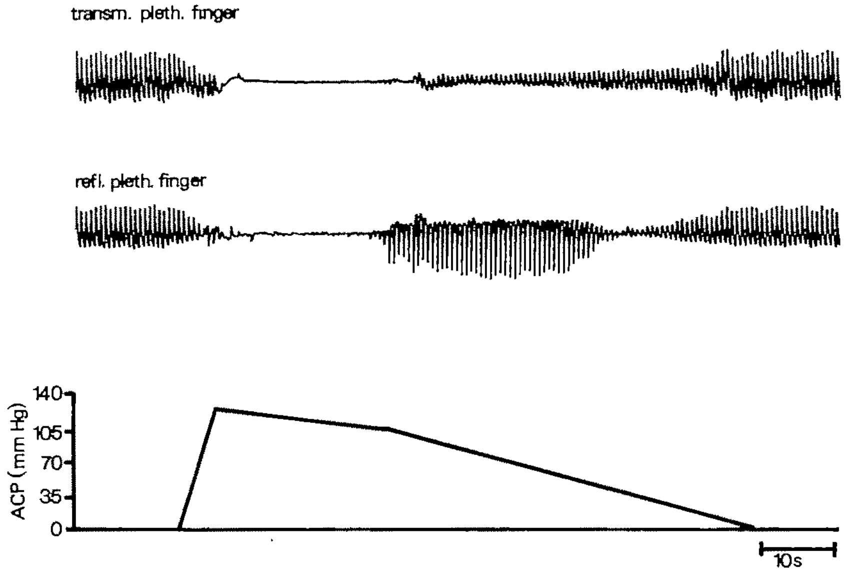

Fig. 2. Difference in waveform between the reflection and the transmission plethysmogram on deflation of the upper arm cuff. Abbreviations as figure 1; transm. pleth. = transmission plethysmogram.

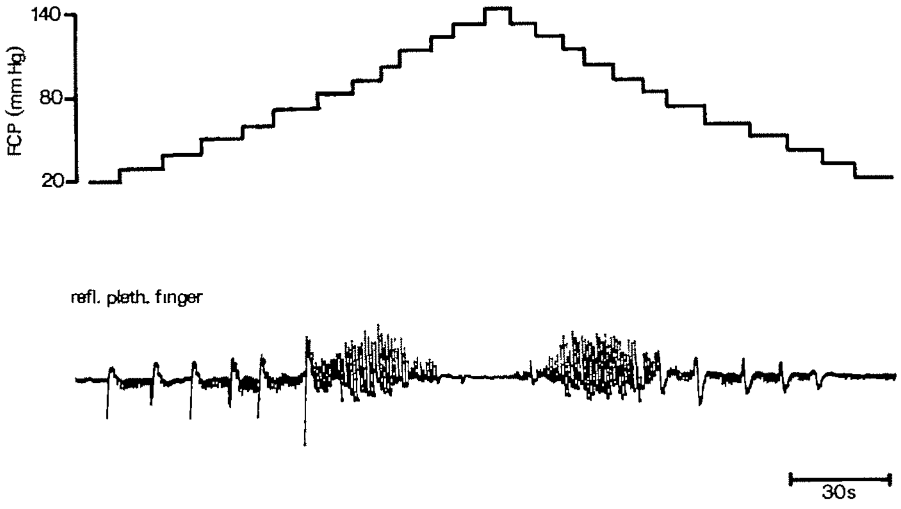

Fig. 3. Reflection plethysmogram from the finger during venous engorgement and stepwise changes in application pressure in the finger cuff. Abbreviations as figure 1; FCP = finger cuff pressure.

that during an arterial pulsation slightly more of the emitted light is absorbed. However, both the erythrocytes present in the blood and the moving vascular walls have reflecting properties also. During an arterial pulsation the erythrocytes orientate in the direction of the flow (Visser et al., 1976) and the vascular walls expand. This results in slightly more reflection of the emitted light. Arterial pulsations therefore have, besides the effect of an increase in absorption, the effect of an increase in reflection of the emitted light. The influence of this dual effect is different for transmission and reflection plethysmography.

In transmission plethysmography reflected light is not detected. The plethysmogram is therefore only determined by changes in transmitted light and during arterial pulsations the increase in absorption and in reflection of the emitted light have the same effect of a decrease in transmitted light. In reflection plethysmography, however, the increase in absorption and the increase in reflection of the emitted light during arterial pulsations have a contrary effect upon the resulting change in emerging light detected. Which of these two contrary effects will predominate depends upon the reflecting properties of the embedding tissue, as we have shown in a previous paper (Nijboer, Dorlas and Mahieu, 1981). This was also demonstrated by Weinman, Hayat and Raviv (1977) in their *in vitro* experiments with isolated blood vessels embedded in agar. The reflection of blood volume pulsations in these vessels was measured against a background which was changed from bright to dark. Two clearly different situations could be distinguished:

(1) against a bright, strongly reflecting background the blood pulsations produced a decrease in the intensity of reflected light, which caused normal wave forms in the plethysmogram.

(2) against a dark, strongly absorbing background the blood pulsations produced an increase in the intensity of reflected light and consequently an inverted plethysmogram.

Against a background of brightness between these two extremes, normal or inverted and sometimes no pulse waves were found.

In our previous paper (Nijboer, Dorlas and Mahieu, 1981) it was demonstrated that the normally perfused finger reflects a considerable amount of light. This must be reflection from the skin and other tissues, because a bloodless finger reflects even more light than a perfused finger. The first series of the present experiments started with a normally perfused finger and against this bright embedding tissue the domination of the absorbing effect of the blood pulsation is bound to cause the normal waveform in the reflection plethysmogram (comparable to condition 1 of Weinman, Hayat and Raviv (1977)). However, with inflation and subsequent deflation of the cuff around the dependent arm to less than systolic pressure, venous engorgement occurs, which may indeed change the optical background from bright to relatively dark. Against this dark embedding tissue the reflecting effect of arterial pulsations may dominate over their absorbing effect, giving rise to inversion of the reflection plethysmogram (compare condition 2 of Weinman).

The increase in amplitude of the inverted waves, following progressive deflation of the arm cuff to the diastolic pressure, can be ascribed mainly to a growing pulse pressure. When the arm cuff pressure decreases to less than 45 mm Hg, the venous engorgement diminishes so that the embedding tissue regains its normal brightness and the inverted waveforms revert to the normal plethysmogram, with increasing amplitude up to the original value.

The transmission plethysmogram always has the normal waveform because venous engorgement only causes less light to be transmitted. Its gradual increase in amplitude on deflation of the upper arm cuff is mainly caused by the growing pulse pressure. The results of the second series of experiments show that the application pressure of the transducer is important to the inversion phenomenon. De Pater, van den Berg and Bueno (1962) have demonstrated that the amplitude increases when the application pressure is increased to 50–60 mm Hg. This was obviously the case with the inverted waveform which was brought about by venous engorgement in the dependent arm at the start of these experiments.

The change from inverted to normal waveforms, when the finger cuff pressure is increased from 70 to 80 mm Hg, must again be a result of change in the optical density of the embedding tissue. The application pressure then passes the local venous engorgement pressure so that part of the venous blood is pushed away. The more venous blood is pushed away the more the amplitude increases, but it decreases again when the application pressure comes near to the systolic pressure. The reverse sequence of events, occurring on subsequent reduction of the finger cuff pressure, is explained in a similar way.

The transmission plethysmogram simultaneously recorded from another finger of the same hand does not show any changes. This only demonstrates that inversion is a local phenomenon restricted to the reflection method.

From these experiments we conclude that inversion is caused by a relative increase in optical density of the surrounding tissue *v.* the arterial vessels. In the finger it is brought about by an interaction between venous engorgement and application pressure. This explains why, during anaesthesia, it may be more easily reproduced when the arm lies well below heart level and the application pressure does not exceed 50–60 mm Hg. It can always be observed, independent of age, sex and state of health of the patients, when in these circumstances arterial pressure is measured in the same arm with an inflatable cuff.

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### REFERENCES

Dorlas, J. C. (1974). Plethysmography in clinical measurement; in *Measurement in Anaesthesia*, Boerhaave series 9, 165. Leiden: University Press.

Johnstone, M. (1974a). Facial vasomotor behaviour. *Br. J. Anaesth.*, 46, 765.

——(1974b). The effects of methyl phenidate on postoperative pain and vasoconstriction. *Br. J. Anaesth.*, 46, 778.

Körner, M. (1974). Untersuchungen mit fotoelectrischen Pulsabnehmern zur Wirkung von vasoaktiver Substanzen in Narkose auf den Fingerpuls. *Anaesthesist*, 23, 209.

Nijboer, J. A., Dorlas, J. C., and Mahieu, H. F. (1981). Photoelectric plethysmography—some fundamental aspects of the reflection and transmission method. *Clin. Phys. Physiol, Meas.*, 2, 205.

Otteni, J. C., Sauvage, M. R., and Gauthier-Lafaye, J. P. (1969). Photoplethysmografie digitale: Application à l'étude de differentes drogues anesthésiques et analgésiques. *Anesth. Analg. Réan.*, 26, 821.

————(1970). Surveillance continue de la circulation péripherique par photopléthysmografie digitale. *Cah. Anesth.*, 18, 735.

————(1971). Valeur du pulsogramme sanglant et non sanglant pour la surveillance de l'analgésie per-operatoire. *Anesth. Analg. Réan.*, 28, 93.

Pater de, J., van den Berg, J., and Bueno, A. A. (1962). A very sensitive photoplethysmograph using scattered light and a photosensitive resistance. *Acta Physiol. Pharmacol. Neerlandica*, 10, 378.

Sara, C. A., and Shanks, C. A. (1978). The peripheral pulse monitor—a review of electrical plethysmography. *Anaesth. Intens. Care*, 6, 226.

Visser, K. R., Lamberts, R., Korsten, H. H. M., and Zijlstra, W. G. (1976). Observations on blood flow related electrical impedance changes in rigid tubes. *Pflügers Arch.*, 366, 289.

Weinman, J., Hayat, A., and Raviv, G. (1977). Reflection photoplethysmography of arterial blood-volume pulses. *Med. Biol. Eng. Comput.*, 15, 22.

## L'ORIGINE DES ONDES INVERSEES DANS LE PLETHYSMOGRAMME REFLECHI

### RESUME

Dans la pléthysmographie réfléchie au doigt, des ondes inversées sont parfois observées, surtout lorsqu'au cours de l'anesthésie, la pression artérielle est mesurée sur le même bras avec un brassard gonflable. Nous avons recherché l'origine de cette inversion dans deux séries d'expériences avec des volontaires. Dans la première série d'expériences, nous avons étudié l'influence de la pression dans le brassard placé au bras et dans la seconde série l'influence de la pression exercée par la transducteur sur le doigt. Nous en concluons que l'inversion des ondes pulsées sur le pléthysmogramme est un phénomène local limité à la méthode réfléchie. Il est provoqué par une augmentation relative de la densité optique des tissus environnants en rapport avec les vaisseaux artériels. Dans le doigt, il est provoqué par un engorgement veineux et est dépendant de la pression appliquée.

## DIE HERKUNFT DER UMGEKEHRTEN WELLENFORMEN BEIM REFLEXIONSPLETHYSMOGRAMM

### ZUSAMMENFASSUNG

Bei der Reflexionsplethysmographie am Finger sind mitunter umgekehrte Pulswellen zu beobachten, besonders wenn während der Narkose der arterielle Blutdruck am selben Arm mit einer aufblasbaren Manschette gemessen wird. Die Herkunft dieser Umkehr wird in zwei Serien von Experimenten an Probanden untersucht. In der ersten Untersuchungs serie wurde der Einfluß des Druckes in der Manschette am Oberarm gemessen und in der zweiten Serie der Einfluß des Anpressdruckes des Überträgers am Finger. Es wird der Schluß gezogen, daß die Umkehr der Pulswellen des Plethysmogramms eine lokale, auf die Reflexionsmethode beschränkte Erscheinung ist. Sie wird durch einen relativen Anstieg der optischen Dichte des umgebenden Gewebes in Bezug zu den arteriellen Gefässen verursacht. Am Finger kommt sie durch die Venenstauung zustande und ist abhängig vom verwendeten Druck.

## EL ORIGEN DE LAS FORMAS INVERTIDAS DE LAS ONDAS EN LA REFLEXIÓN DEL PLETISMOGRAMA

### SUMARIO

A veces, se observan ondas pulsatorias invertidas en el dedo en la pletismografía de reflexión, en particular cuando, en el curso de la anestesia, se mide la presión arterial en el mismo brazo con un brazal inchable. El origen de esta inversión es objeto de investigaciones en dos series de experimentos en voluntarios. En la primera serie de experimentos, se indagó la influencia de la presión en el brazal superior y en la segunda serie, se investigó la influencia de la presión de aplicación del transductor en el dedo. Se concluye que la inversión de las ondas pulsatorias del pletismograma constituye un fenómeno local que se restriñe al método de reflexión. Lo ocasiona un aumento relativo de la densidad óptica del tejido circundante en relación con los vasos arteriales. En el dedo, se produce a raíz de la congestión de las venas y depende de la presión aplicada.

Br. J. Anaesth. (1982), 54, 1295

# PRE- AND POSTJUNCTIONAL BLOCKING EFFECTS OF AMINOGLYCOSIDE, POLYMYXIN, TETRACYCLINE AND LINCOSAMIDE ANTIBIOTICS

Y. N. SINGH, I. G. MARSHALL AND A. L. HARVEY

## SUMMARY

The effects of seven antibiotics (streptomycin, amikacin, polymyxin B, lincomycin, clindamycin, tetracycline and oxytetracycline) were compared with those of magnesium, tubocurarine and lignocaine in the frog sciatic nerve – sartorius muscle preparation, using intracellular recording techniques. All compounds except tubocurarine decreased end-plate potential quantal content. The prejunctional effects of magnesium, streptomycin, amikacin, polymyxin B and oxytetracycline (but not the other drugs) were well reversed by increasing the calcium concentration. At concentrations which depressed quantal content, only magnesium, tetracycline and oxytetracycline did not reduce postjunctional sensitivity. Further postjunctional effects of the drugs were revealed by alterations in the time-courses of end-plate potentials. All the drugs tested except magnesium, tubocurarine and lincomycin produced changes in muscle action potentials. None of the compounds had anticholinesterase activity. The results confirm that aminoglycoside, polymyxin, tetracycline and lincosamide antibiotics produce neuromuscular block by a combination of both pre- and postjunctional actions.

It has been known for more than 25 years that certain antibiotics can induce paralysis of skeletal muscle. Clinical and experimental studies have shown that muscle paralysis can be caused by four main classes of antibiotic: the aminoglycosides (streptomycin and neomycin), the polymyxins, the tetracyclines and the lincosamides (lincomycin and clindamycin). However, the underlying mechanisms of action of all these groups have not been fully elucidated (for reviews see Pittinger and Adamson, 1972; Sanders and Sanders, 1979; Singh, Marshall and Harvey, 1980; Sokoll and Gergis, 1981).

Neuromuscular mechanisms suggested to be involved include: (1) reduction of the amount of acetylcholine released from the nerve terminals in response to motor nerve stimulation, (2) reduction of the sensitivity of the postjunctional acetylcholine receptors by block of these recognition sites, and (3) reduction of end-plate ionic conductance by blockade of the receptor-activated ion channels. Any of these mechanisms, either alone or in combination, would reduce the end-plate potential (e.p.p.) below the level at which it can initiate a muscle action potential and hence muscle contraction would cease. Additionally, antibiotics may possess a local anaesthetic action which would prevent nerve action potentials from invading the motor nerve terminals, or block muscle action potentials and hence contraction, or have both these effects.

The purpose of the present study was to determine the effects of one or more antibiotics from the above four classes on the different physiological processes involved in neuromuscular transmission in the frog, using intracellular recording techniques, and hence establish more precisely their mechanism of muscle paralysis.

## METHODS

### *Frog sciatic nerve–sartorius muscle preparation*

The isolated sciatic nerve–sartorius muscle preparation from *Rana temporaria* (during summer) or *Rana pipiens* (during winter) was used as this muscle possesses large muscle fibres, allowing long periods of stable penetration with microelectrodes to be maintained through several changes of drug solution. No difference was found between results obtained on the two species. The preparations were pinned to a resin-coated 10-ml Perspex tissue bath and bathed in normal frog Ringer solution (sodium chloride 111 mmol litre$^{-1}$; potassium chloride 2 mmol litre$^{-1}$; sodium bicarbonate 2 mmol litre$^{-1}$; calcium chloride 2 mmol litre$^{-1}$; Tris 1 mmol litre$^{-1}$) or in high magnesium

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(8 mmol litre$^{-1}$) – low calcium (1 mmol litre$^{-1}$) Ringer solution ("high magnesium Ringer"). The pH of the solution was 7.3 and the experiments were conducted at room temperature (16–21 °C).

*Intracellular recording*

Membrane potentials were measured between an intracellular glass microelectrode filled with potassium chloride 3 mol litre$^{-1}$ or potassium acetate 2 mol litre$^{-1}$ (5–15 Ω resistance) and a silver–silver chloride reference electrode. A high impedance unity gain electrometer (WPI M4A or M701) amplified the signal, which was displayed on a storage oscilloscope and on an oscilloscope fitted with an oscilloscope camera. Filmed records were enlarged and measured by hand.

The preparations were observed at a magnification of 300 times with a binocular microscope fitted with a Leitz UM 20/0.33 long working distance objective. End-plate regions were localized by following nerve twigs and penetrating muscle fibres until spontaneously occurring miniature end-plate potentials (m.e.p.p.) with rise times of less than 1.5 ms could be recorded. Cells were rejected if the initial resting membrane potential was more positive than −75 mV.

To study evoked transmitter release the sciatic nerve was stimulated at a frequency of 0.5 Hz through a bipolar platinum electrode by rectangular pulses of 0.2 ms duration and of a voltage greater than that required to produce end-plate potentials (e.p.p.). Only one concentration of test drug was used in each experiment and after each addition of drug or change of solution at least 20 min equilibration was allowed before recordings were made.

The effects of the antibiotics were studied on e.p.p. quantal content (that is, the number of packets of acetylcholine released by a single nerve impulse) to assess prejunctional activity; the amplitude of the spontaneously occurring miniature end-plate potentials (m.e.p.p.) to assess postjunctional activity; and end-plate potential time-course to provide an indication of possible activity on end-plate ion channel properties.

At least 50 m.e.p.p. and 150 e.p.p. were recorded from each end-plate region for each measurement. All values of m.e.p.p. and e.p.p. amplitudes were corrected to a standard membrane potential of −80 mV (Katz and Thesleff, 1957) and e.p.p. were also corrected for non-linear summation (Martin, 1955), assuming a transmitter reversal potential of −15 mV. Whenever the postjunctional blocking action of a compound under study was sufficiently low to allow m.e.p.p. to be recorded, e.p.p. quantal content was determined by the ratio of the mean amplitudes of e.p.p. and m.e.p.p. However, when m.e.p.p. were reduced to the noise level of the recording system, the method of variance (del Castillo and Katz, 1954) was used for estimation of quantal content, although this method overestimates quantal content at high levels of release (Miyamoto, 1975).

Two types of experiment to assess effects on quantal content were performed: in normal frog Ringer solution in which transmitter release was not impaired by other drugs, and in high magnesium Ringer solution in which evoked transmitter release had been reduced to a low level. In addition, it is known that aminoglycosides exert their prejunctional blocking action by competing with calcium ions for sites on the nerve terminal in a manner similar to magnesium ions (Elmqvist and Josefsson, 1962; Prado, Corrado and Marseillan, 1978; Maeno and Enomoto, 1980). Therefore, in the present study we have attempted to assess if the effects of the other three classes of antibiotic tested are a result of a similar competition with calcium ions by examining the effects of the antibiotics on end-plate potential quantal content at four different calcium concentrations. In preparations in which three changes of calcium concentration were made, penetrations were maintained for 2.5–3 h.

The rise times of m.e.p.p. and e.p.p. were measured from the first discernible depolarization to the peak of the response and the time to half decay was measured from the peak of the response to 50% repolarization. The m.e.p.p. frequency per second was calculated from the number of m.e.p.p. measured × 1000 divided by the number of oscilloscope sweeps × the sweep time (ms).

To assess local anaesthetic activity of the antibiotics, their effects were studied on the configuration of muscle action potentials. Muscle action potentials were elicited by inserting a second microelectrode into a fibre about 600 μm from the recording electrode and stimulating with a rectangular 0.2-ms pulse of strength sufficient to trigger an action potential.

*Anticholinesterase activity*

The anticholinesterase activity of the antibiotics was assessed using the colorimetric cholinesterase assay described by Ellman and others (1961). Homogenates of frog sartorius muscles (about 5 mg wet weight/ml) were used as the source of cholinesterase with acetylcholine iodide as substrate.

### *Statistics*

The results are presented in the text as means ± SEM of experiments on at least five separate preparations for each drug concentration. Statistical comparisons of means shown in the tables were made by the Mann–Whitney *U* test, values of $P < 0.05$ being regarded as significant.

Multiple comparisons of slope values for log calcium concentration against log quantal content were made by linear regression analysis of covariance and the Newman–Keuls multiple range test (Zar, 1974). Comparison of single pairs of slope values was made by Student's *t* test.

### *Drugs*

Drugs used were amikacin sulphate (Mead Johnson), lignocaine hydrochloride (Astra); acetylthiocholine iodide, oxytetracycline hydrochloride, streptomycin sulphate, tetracycline hydrochloride, tubocurarine chloride (all Sigma); clindamycin hydrochloride, lincomycin hydrochloride (both Upjohn) and polymyxin B sulphate (Wellcome or Sigma).

The drug solutions were freshly made before use by dissolving them in the appropriate physiological saline. Drugs were applied by total replacement of the tissue bath fluid or, in the studies on m.e.p.p., by local microperfusion to the end-plate region under investigation (Manthey, 1966).

## RESULTS

### *Effects on m.e.p.p. amplitude and frequency*

The effects of seven antibiotics (streptomycin, amikacin, polymyxin B, lincomycin, clindamycin, tetracycline and oxytetracycline) on the amplitude and frequency of m.e.p.p. were assessed in preparations paralysed by bathing in high magnesium Ringer. The effects of tubocurarine (used as a predominantly postjunctionally active drug), lignocaine (used as a local anaesthetic drug) and additional magnesium (used as a predominantly prejunctionally active agent) were also determined.

With all drugs tested there was a gradual decline in m.e.p.p. amplitude, indicating a postjunctional blocking action, starting from the time of application and reaching a constant mean amplitude after 15–20 min. With the exception of magnesium 4 mmol litre$^{-1}$, tetracycline 0.5 mmol litre$^{-1}$ and oxytetracycline 0.5 mmol litre$^{-1}$, the decreased amplitude was significantly different from control (fig. 1).

With all drugs apart from lignocaine and clin-

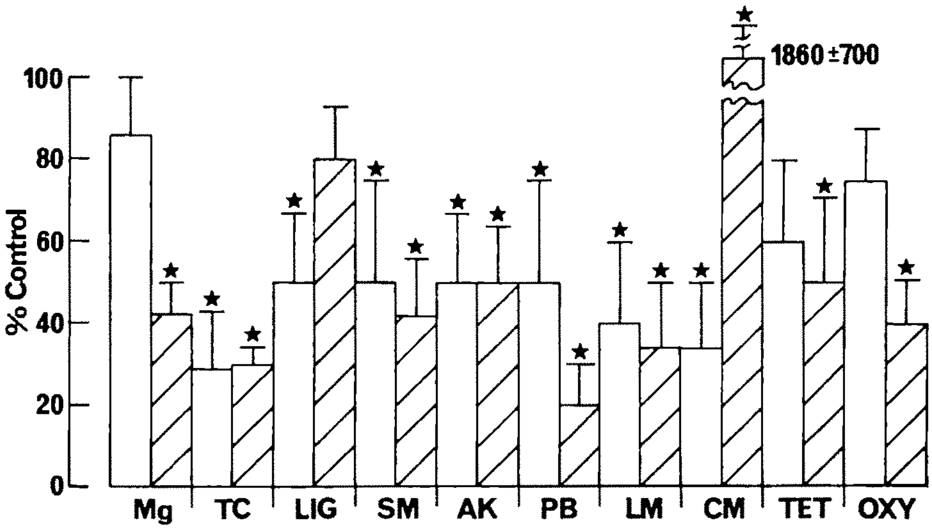

FIG. 1. Effects of the 10 test drugs on amplitude (open columns) and frequency (hatched columns) of miniature end-plate potentials (m.e.p.p.) recorded in high-magnesium Ringer solution. Drug concentrations were: magnesium (Mg) 4.0 mmol litre$^{-1}$; tubocurarine (TC) 1.1 μmol litre$^{-1}$; lignocaine (LG) 0.35 mmol litre$^{-1}$; streptomycin (SM) 0.4 mmol litre$^{-1}$; amikacin (AK) 0.43 mmol litre$^{-1}$; polymyxin B (PB) 4.6 μmol litre$^{-1}$; lincomycin (LM) 3.2 mmol litre$^{-1}$; clindamycin (CM) 0.71 mmol litre$^{-1}$; tetracycline (TET) 0.5 mmol litre$^{-1}$; and oxytetracycline (OT) 0.5 mmol litre$^{-1}$. Values are expressed as % of predrug control values obtained in the same fibres. Control amplitudes ranged from 0.4 to 0.8 mV and control frequencies ranged from 0.5 to 2.3 m.e.p.p. s$^{-1}$. Each column represents the mean of experiments on at least six preparations; SEM are indicated by the vertical bars. *Significantly different ($P < 0.05$) from control values.

damycin, the decrease in m.e.p.p. amplitude was accompanied by a parallel decline in the frequency of m.e.p.p. (fig. 1). Spontaneous release stabilized at a new level 15–20 min after the start of drug application. In preparations treated with clindamycin 0.71 mmol litre$^{-1}$, m.e.p.p. frequency increased immediately after the onset of drug application. This increase in frequency was eight times control after 15 min and more than 17 times control after 25 min and was accompanied by a rapid diminution of amplitude so that it was difficult to distinguish small m.e.p.p. from baseline noise.

*Effects on e.p.p. quantal content*

The effects of seven antibiotics (streptomycin, amikacin, polymyxin B, lincomycin, clindamycin, tetracycline and oxytetracycline) and three control drugs (magnesium, tubocurarine and lignocaine) on e.p.p. quantal content were determined.

A control value of 296 ± 33 for e.p.p. quantal content in the absence of drugs was obtained from sartorius muscle preparations that had been cut to prevent twitching (Lambert et al., 1981). This represents the number of packets of acetylcholine normally released by a single nerve impulse.

Concentrations of paralysing drugs were chosen to be the least that consistently allowed intracellular recording, that is no muscle contraction in response to nerve stimulation, after 20–30 min equilibration time. In muscle paralysed by the predominantly prejunctional blocking substance magnesium (15 mmol litre$^{-1}$), the amplitudes of e.p.p. fluctuated randomly and the quantal content was 11 ± 2. In the presence of the predominantly postjunctional blocking drug tubocurarine (4 µmol litre$^{-1}$), the fluctuations of e.p.p. amplitude were slight and quantal content was 248 ± 50, which was not significantly different from the value obtained from the cut muscle preparations. E.p.p. quantal content was depressed by the local anaesthetic lignocaine (0.62 mmol litre$^{-1}$), but greater concentrations resulted in a sudden abolition of all e.p.p. activity. This effect was probably a result of a block of nerve conduction so that e.p.p. could not be elicited.

In the presence of streptomycin 0.61 mmol litre$^{-1}$ or amikacin 1.7 mmol litre$^{-1}$, fluctuations of the amplitude of e.p.p. were similar to those recorded in the presence of magnesium and values for quantal contents were similar to those recorded in magnesium (table I). In the presence of the other antibiotics (polymyxin B 9 µmol litre$^{-1}$, lincomycin 9.7 mmol litre$^{-1}$, clindamycin 0.71 mmol litre$^{-1}$, tetracycline 2 mmol litre$^{-1}$ and oxytetracycline 2 mmol litre$^{-1}$), the variance in amplitudes of e.p.p. was intermediate between that found in magnesium and in tubocurarine, and quantal content ranged from 35 to 106 (table I). E.p.p. could be recorded from only some end-plates in clindamycin-paralysed muscles, and with concentrations of clindamycin greater than 0.71 mmol litre$^{-1}$ no e.p.p. activity could be measured. The pattern of clindamycin-induced block was similar to that seen with lig-

TABLE I. *Effects of the 10 test drugs on mean e.p.p. quantal content in normal and high-magnesium Ringer solution and the effects of different calcium concentrations on the quantal content in normal Ringer solution. Values represent the mean ± SEM of experiments on four to six preparations. *Significantly different ($P < 0.05$) from control; †slope value significantly different ($P < 0.05$) from that of magnesium; ‡Control quantal contents in high-magnesium Ringer solution ranged from 3.5 to 23.7*

| | Normal Ringer solution | | | High-magnesium Ringer soln | |
|---|---|---|---|---|---|
| Test drug | Concentration | Mean e.p.p. quantal content | Slope of log quantal content: log [Ca] relationship | Concentration | % Reduction of quantal content‡ |
| Control (cut muscle) | | 296 ± 33 | — | — | — |
| Magnesium | 15 mmol litre$^{-1}$ | 11 ± 2* | 2.57 ± 0.49 | 4 mmol litre$^{-1}$ | 76 ± 4* |
| Tubocurarine | 4 µmol litre$^{-1}$ | 248 ± 50 | 0.53 ± 0.04† | 1.1 µmol litre$^{-1}$ | 0 ± 24 |
| Lignocaine | 0.62 mmol litre$^{-1}$ | 198 ± 20* | 0.86† | 0.35 mmol litre$^{-1}$ | 26 ± 13 |
| Streptomycin | 0.61 mmol litre$^{-1}$ | 16 ± 3* | 2.35 ± 0.57 | 0.40 mmol litre$^{-1}$ | 54 ± 6* |
| Amikacin | 1.7 mmol litre$^{-1}$ | 12 ± 2* | 2.26 | 0.43 mmol litre$^{-1}$ | 42 ± 16* |
| Polymyxin B | 9 µmol litre$^{-1}$ | 106 ± 14* | 2.31 ± 0.35 | 4.6 µmol litre$^{-1}$ | 65 ± 8* |
| Lincomycin | 9.7 mmol litre$^{-1}$ | 75 ± 5* | 0.95 ± 0.10† | 3.2 mmol litre$^{-1}$ | 35 ± 9* |
| Clindamycin | 0.71 mmol litre$^{-1}$ | 74 ± 14* | 1.25 ± 0.13† | 0.71 mmol litre$^{-1}$ | 52 ± 25* |
| Tetracycline | 2 mmol litre$^{-1}$ | 35 ± 3* | 1.36 ± 0.09† | 0.50 mmol litre$^{-1}$ | 60 ± 11* |
| Oxytetracycline | 2 mmol litre$^{-1}$ | 56 ± 4* | 1.81 ± 0.14 | 0.50 mmol litre$^{-1}$ | 37 ± 6* |

nocaine.

In high-magnesium Ringer, lower concentrations of the drugs than those used in normal Ringer were used as, in most cases, the concentrations used in normal Ringer reduced e.p.p. amplitude to such an extent that accurate measurement of responses was not possible. The concentrations used were two to four times less than those in the normal Ringer experiments, but in the case of clindamycin it was possible to use the same concentration as in the normal Ringer experiments (table I). Smaller concentrations of clindamycin did not affect quantal content and greater concentrations blocked nerve conduction. Apart from tubocurarine and lignocaine, all drugs tested significantly reduced quantal content. The relative effectiveness of the antibiotics was similar to that found in normal Ringer solution.

With all drugs tested, an increase in the calcium concentration increased quantal content, but the relationship between calcium and quantal content differed with different drugs (fig. 2). Log–log slopes of quantal content against calcium concentration yielded straight lines (Dodge and Rahamimoff, 1967) with different slopes for different drugs (table I). Magnesium-paralysed preparations gave the largest value for the slope (2.57), whereas tubocurarine-paralysed preparations had the smallest value (0.53). Other values were between these two extremes (table I). The slopes were ranked and the slope for magnesium was compared with those of all the other drugs by linear regression analysis of covariance and Newman–Keuls multiple range test. This test is a ranking test that takes into account the scatter of the data for all the compounds tested when comparing the relative positions of a pair of compounds in the rank order. This reduces the probability of type 1 statistical errors. A large number of comparisons can be made using this test, but for the sake of clarity only the values related to the magnesium slope are included. The results are expressed as *P* values to indicate the level of probability of difference from magnesium and are as follows: tubocurarine, lignocaine and lincomycin ($P < 0.05$); clindamycin and tetracycline ($P < 0.2$); oxytetracycline ($P < 0.5$); polymyxin B, streptomycin and amikacin ($P > 0.5$). Individual pairs of slope values were also compared using Student's *t* test which disregards the data from other compounds tested in the same way. Using this test the slope for magnesium was not significantly different from those for streptomycin, amikacin, polymyxin B, or oxytetracycline, but was significantly greater than those of the remaining compounds ($P < 0.05$). Other pairs of drugs tested showed that the slope for oxytetracycline was significantly greater than that for tetracycline, but that no difference existed between lincomycin and clindamycin, and between polymyxin B and oxytetracycline. Thus, in both statistical tests streptomycin, amikacin, polymyxin B and oxytetracycline were not significantly different from magnesium and hence it is likely that competition with calcium plays a part in the prejunctional action of these four agents.

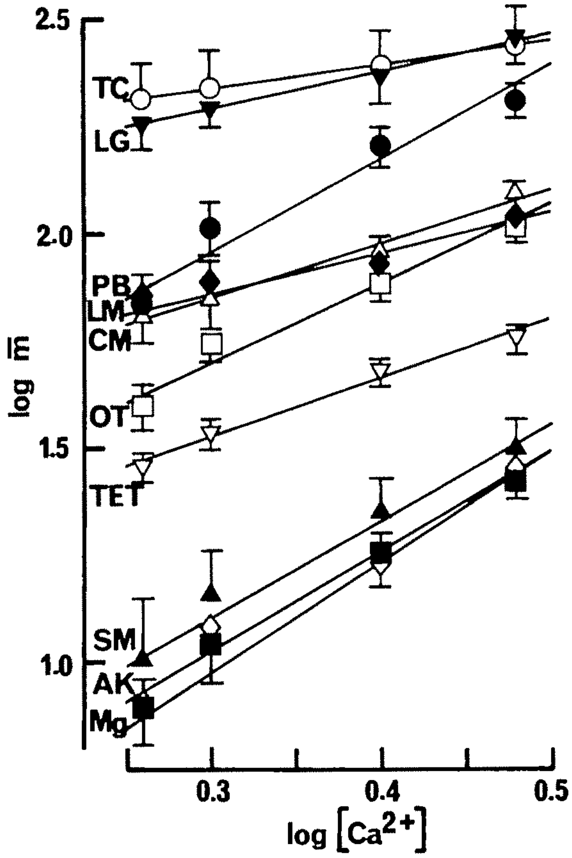

FIG. 2. Log–log plot of the effect of different calcium concentrations in normal frog Ringer solution on mean e.p.p. quantal content ($\bar{m}$) recorded in preparations paralysed with tubocurarine 4 μmol litre$^{-1}$ (TC, ○), lignocaine 0.62 mmol litre$^{-1}$ (LG, ▼), polymyxin B 9 μmol litre$^{-1}$ (PB, ●), lincomycin 9.7 mmol litre$^{-1}$ (LM, ◆), clindamycin 0.71 mmol litre$^{-1}$ (CM, △), oxytetracycline 2 mmol litre$^{-1}$ (OT, □), tetracycline 2 mmol litre$^{-1}$ (TET, ▽), streptomycin 0.61 mmol litre$^{-1}$ (SM, ▲), amikacin 1.7 mmol litre$^{-1}$ (AK, ◇) and $Mg^{2+}$ 15 mmol litre$^{-1}$ (Mg, ■). Points represent the mean (± SEM) of experiments on four or five preparations. Lines through the points were derived by linear regression (slopes are given in table I).

### *Effects on time-course of e.p.p. and m.e.p.p. and on cholinesterase*

The effects of the antibiotics and magnesium, tubocurarine and lignocaine on the time-course of m.e.p.p. and e.p.p. were determined in high-magnesium Ringer and in normal Ringer. The effects of the drugs on both e.p.p. and m.e.p.p. were qualitatively the same in both types of experiments. Figure 3 summarizes the effects on e.p.p. time-course in high-magnesium Ringer. Polymyxin B, clindamycin and lignocaine reduced both rise time and time to 50% decay, whereas the other drugs had no effect on rise time but increased time to 50% decay. Amikacin was not tested in this way.

Effects on time-course could not be ascribed to effects on cholinesterase as none of the compounds possessed significant anticholinesterase activity in concentration ranges which produced marked effects on the time-course of potentials.

### *Effects on muscle action potentials*

With the exception of magnesium, tubocurarine and lincomycin, all compounds in concentration ranges similar to those inducing neuromuscular paralysis produced marked changes in muscle action potential parameters (fig. 4). Magnesium 15 mmol litre$^{-1}$, tubocurarine 4 $\mu$mol litre$^{-1}$ and lincomycin 4–16 mmol litre$^{-1}$ had no significant effect on overshoot, maximum rate of rise or maximum rate of fall of action potentials. Amikacin was not tested.

Tetracycline 2 mmol litre$^{-1}$ and oxytetracycline 2 mmol litre$^{-1}$ significantly reduced both maximum rate of rise and maximum rate of fall of action potentials. Overshoot was not significantly affected. The effects on rates of rise and fall developed progessively within the first 10–20 min of exposure and then remained constant during the remainder of the period of exposure.

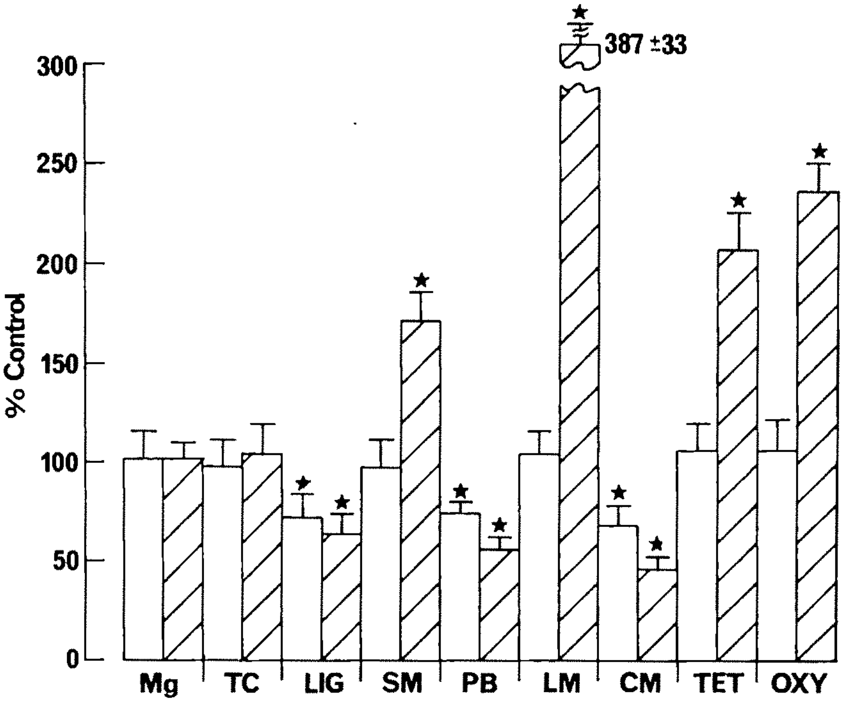

FIG. 3. Effects of nine test drugs on rise time (open columns) and time to 50% decay (hatched columns) of e.p.p. recorded in high-magnesium solution. Drugs used were as given in the legend to figure 1. Values are expressed as % of predrug control values obtained in the same fibres. Control rise times ranged from 1.31 to 1.37 ms and control times to 50% decay ranged from 2.66 to 3.05 ms. Each column represents the mean of experiments on at least six preparations; SEM are indicated by the vertical bars. *Significantly different ($P < 0.05$) from control values.

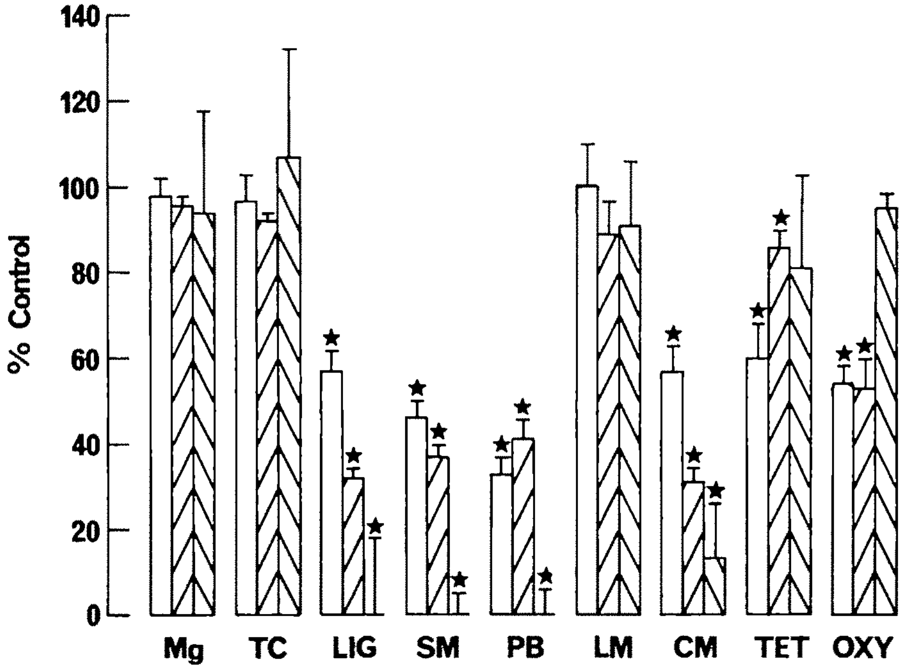

FIG. 4. Effects of nine test drugs on overshoot, maximum rates of rise and of fall of muscle action potentials. Lefthand columns: maximum rate of rise; middle columns: maximum rate of fall; right hand columns: overshoot. Drug concentrations were: magnesium (Mg) 15 mmol litre$^{-1}$; tubocurarine (TC) 4 $\mu$mol litre$^{-1}$; lignocaine (LG) 1.4 mmol litre$^{-1}$; streptomycin (SM) 2.4 mmol litre$^{-1}$; polymyxin B (PB) 43 $\mu$mol litre$^{-1}$; lincomycin (LM) 16 mmol litre$^{-1}$; clindamycin (CM) 1.4 mmol litre; tetracycline (TET) 2 mmol litre$^{-1}$; and oxytetracycline (OT) 2 mmol litre$^{-1}$. Measurements were made after 60 min exposure to the test drugs and values are expressed as % of predrug control values obtained in the same fibres. Control values for maximum rate of rise ranged from 369 to 464 V s$^{-1}$; for maximum rate of fall from 106 to 133 V s$^{-1}$; and for overshoot from 28 to 38 mV. Each column represents the mean of experiments on at least six preparations; SEM are indicated by the vertical bars. *Significantly different ($P < 0.05$) from control values.

Clindamycin 2.8 mmol litre$^{-1}$ produced a biphasic effect on action potential configuration. During the first 20–30 min of exposure, maximum rates of rise and fall were reduced and the overshoot became progressively smaller until the action potential failed to reach the zero potential at around 30 min. Further exposure to clindamycin resulted in a secondary increase in the maximum rate of rise from its depressed level until after 60 min the rate of rise was greater than that of control action potentials. There was no parallel secondary increase in the maximum rate of fall or overshoot, which remained depressed. After 60–90 min it became impossible to generate action potentials and at this time a stable membrane potential could not be recorded. At lower concentrations of clindamycin (0.7–1.4 mmol litre$^{-1}$) similar depressions of overshoot, maximum rates of rise and fall were observed without the secondary increase in the maximum rate of rise. Action potentials could still be generated 120 min after application of drug.

Streptomycin 1.2–2.4 mmol litre$^{-1}$, polymyxin B 0.043–0.086 mmol litre$^{-1}$ and lignocaine 1.4 mmol litre$^{-1}$ also decreased maximum rates of rise and fall and reduced the overshoot (fig. 4). Action potentials usually failed to reach zero potential at the greater concentrations of the drugs. With these drugs the reduction in action potential parameters progressed until no action potentials could be generated, and there was no secondary increase in the rates of rise.

Except with clindamycin, no changes in resting membrane potentials were noted with the compounds, even at the greatest concentrations used.

## DISCUSSION

The results of the present study confirm and extend those from previous studies by showing that members of the four classes of antibiotics tested possess relatively different effects on the various stages of neuromuscular transmission.

The concentrations used in the study were those that caused complete cessation of muscle twitching in response to nerve stimulation in normal solution. Concentrations two to four times smaller were used in the magnesium-paralysed preparations. In the main, these concentrations are greater than the "maximum therapeutic level" as recently used by Caputy, Kim and Sanders (1981). Nevertheless, it is important to determine mechanisms of side-effects of drugs at concentrations greater than those normally attained in the body. In this way an attempt is made to account for different susceptibilities of individual patients or different animal models to the drugs.

The neuromuscular blockade produced by the aminoglycosides streptomycin and amikacin was similar to that produced by a high concentration of $Mg^{2+}$, that is it was associated with a large significant decrease in evoked release of acetylcholine and with a smaller but still significant decrease in postjunctional receptor sensitivity and spontaneous release. These findings agree with results obtained in the mouse diaphragm with streptomycin (Singh, Marshall and Harvey, 1979) and amikacin (Singh, Marshall and Harvey, 1978a) and in the rat hemidiaphragm preparation with neomycin and gentamicin (Elmqvist and Josefsson, 1962; Caputy, Kim and Sanders, 1981). The effects of altering the external $Ca^{2+}$ concentration on the neuromuscular blockade induced by the aminoglycosides were similar to the effects on $Mg^{2+}$-induced blockade, confirming the suggestion that the aminoglycosides reduce transmitter release by a mechanism similar to that of $Mg^{2+}$ involving a competition for $Ca^{2+}$ binding sites on the nerve terminal (Prado, Corrado and Marseillan, 1978; Maeno and Enomoto, 1980).

The effects of streptomycin on m.e.p.p. amplitude and on e.p.p. and m.e.p.p. time-course suggest that postjunctional effects could be attributable to either receptor or end-plate ion channel blockade. Channel blockade is usually measured from changes of the decay characteristics of end-plate currents measured under voltage clamp conditions, but changes in end-plate current time-course will be reflected to some extent in the time-course of end-plate potentials. Voltage clamp studies have shown that streptomycin possesses end-plate ion channel blocking activity in the mouse (Pennefather and Quastel, 1980), but not in the snake (Fiekers and Parsons, 1980). In the present experiments the aminoglycosides had no effect on muscle cholinesterase activity and hence the prolongation of e.p.p. and m.e.p.p. cannot be explained by such an action.

As previously found in other preparations (Sokoll and Diecke, 1969; Diecke, Westecker and Vogt, 1971) streptomycin altered the time-course of action potentials, indicating that it has blocking effects on electrically excitable membrane ion channels. The concentrations required were greater than those causing neuromuscular blockade. Although nerve terminals are probably more sensitive than muscle fibres to any local anaesthetic action, it is unlikely that such an action will contribute to the neuromuscular blocking action, as the characteristics of the neuromuscular block were quite different from that produced by the local anaesthetic lignocaine.

Paralysing concentrations of polymyxin B reduced quantal content, although not to as great extent as $Mg^{2+}$ or the aminoglycosides. Previously, experiments involving collection and assay of acetylcholine from isolated rat diaphragm (Brownlee, 1957; Wright and Collier, 1976a) and frog gastrocnemius preparations (Dretchen et al., 1972) have failed to show any effects of polymyxin B or colistin (polymyxin E) on acetylcholine release. However, intracellular recording methods are probably more sensitive than transmitter collection experiments, and the finding of decreased acetylcholine release in the presence of polymyxin B is in accord with results obtained in the mouse diaphragm preparation (Singh, Marshall and Harvey, 1979) and in the cut frog cutaneous pectoris muscle (Durant and Lambert, 1981). The slope of the log $Ca^{2+}$ concentration against log quantal content in polymyxin B was similar to that of magnesium and the aminoglycosides, suggesting a prejunctional competition with calcium. The fact that polymyxin B-induced blockade of muscle twitch is not well reversed by increased $Ca^{2+}$ (Singh, Harvey and Marshall, 1978) may indicate that the prejunctional action of the compound on quantal content is less important than other actions in reducing twitch tension.

As shown in the rat diaphragm (Brownlee, 1957; Lüllmann and Reuter, 1960; Wright and Collier, 1976a; Caputy, Kim and Sanders, 1981) and polymyxin B reduced postjunctional sensitivity. Since polymyxin B markedly reduced e.p.p. and m.e.p.p. time-courses, it is probable that the drug at least partially decreases postjunctional sensitivity by blocking end-plate ion channel conductance, as has been shown in voltage-clamped snake and frog muscle (Fiekers and Parson, 1980; Durant and Lambert, 1981; Fiekers, 1981).

Polymyxin B also produced effects on muscle action potentials, although this was seen only in concentrations greater than those needed to induce muscle paralysis. Wright and Collier (1976a) postulated that the local anaesthetic action of polymyxin B plays a large part in the muscle-paralysing actions of the antibiotic. However, the characteristics of the neuromuscular block produced by polymyxin B were quite different from those produced by the local anaesthetic lignocaine. Hence it is likely that the effects of polymyxin B on neuromuscular transmission are at least as important as the local anaesthetic activity of the compound.

The muscle-paralysing effects of tetracyclines have been studied less extensively than those of other types of antibiotics (Pittinger and Adamson, 1972). In the present study tetracycline and oxytetracycline decreased e.p.p. quantal content but did not significantly affect m.e.p.p. amplitude, suggesting that these antibiotics have predominantly prejunctional blocking actions. However, an action on muscle contractility may be as important as the neuromuscular blocking properties, since it was previously shown that tetracycline and oxytetracycline block both indirectly and directly stimulated mouse diaphragm preparations (Singh, Harvey, Marshall, 1978) and both drugs were found to depress muscle action potentials at the same concentration that decreased quantal content.

There were differences between the effects of the tetracyclines used in the present study and the primarily postjunctional effects previously reported for rolitetracycline (Wright and Collier, 1976a). In addition, there was a suggestion of differences in the

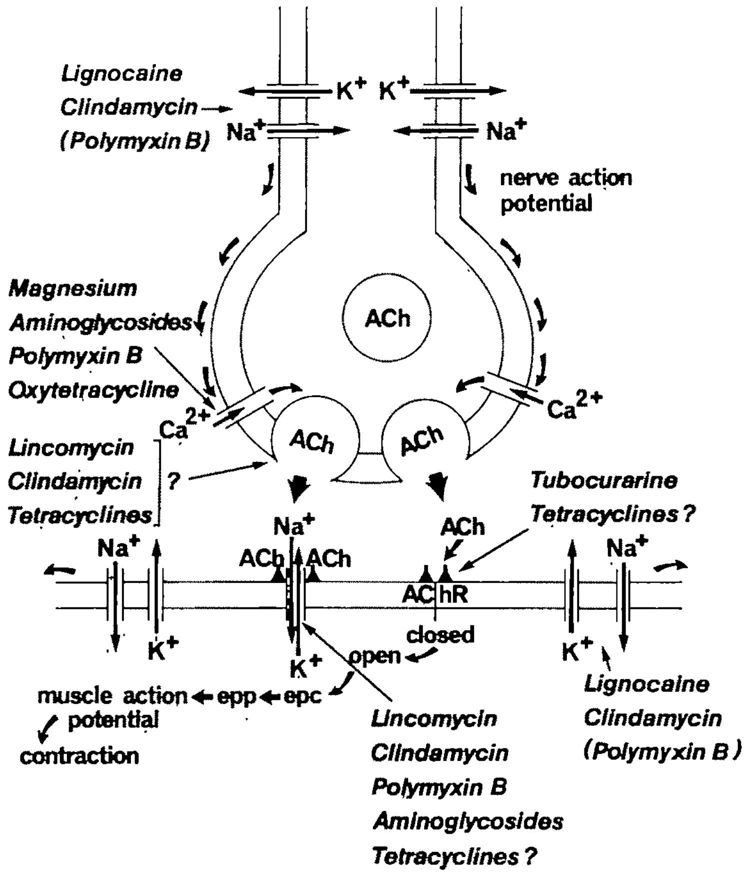

FIG. 5. Schematic representation of neuromuscular transmission and suggested sites of action of some antibiotics.

effects of tetracycline and oxytetracycline. For example, the action of oxytetracycline on quantal content was as $Ca^{2+}$-sensitive as that of $Mg^{2+}$, whereas the action of tetracycline appeared to be less $Ca^{2+}$-sensitive than oxytetracycline. This suggests that tetracycline may act differently from $Mg^{2+}$ at the nerve terminal, while oxytetracycline may act in a fashion somewhat similar to $Mg^{2+}$. Supportive evidence for this suggestion is that, in the isolated mouse phrenic nerve–hemidiaphragm preparation oxytetracycline, but not tetracycline, is reversed by doubling the concentration of $Ca^{2+}$ (Singh, Harvey and Marshall, 1978) or by 3, 4-diaminopyridine (Singh, Marshall and Harvey, 1978b).

Despite the close chemical similarity of lincomycin and clindamycin there is evidence suggesting that these two lincosamides produce muscle paralysis by different mechanisms (Wright and Collier, 1976b; Rubbo, Gergis and Sokoll, 1977; Singh, Harvey and Marshall, 1978). In the present study, both drugs had pre- and postjunctional blocking actions. The prejunctional effects were not magnesium-like as they were significantly less affected than magnesium by alterations in external $Ca^{2+}$ concentration. The prejunctional effects of clindamycin were detectable only in a very narrow concentration range and, as reported previously (Rubbo, Gergis and Sokoll, 1977), were accompanied by an increase in m.e.p.p. frequency, which was not seen with lincomycin.

The effects of clindamycin on the time-course of e.p.p. and m.e.p.p. were qualitatively similar to those of polymyxin B, suggesting, as has been shown by Fiekers, Marshall and Parsons (1979), that the compound blocks end-plate channel conductance. The prolongation of e.p.p. and m.e.p.p. by lincomycin was not explicable by an anticholinesterase action of the compound, but may be explained by the kinetics of the blocking action of the compound on channel conductance (Fiekers, Marshall and Parsons, 1979).

At neuromuscular blocking concentrations lincomycin had no detectable effect on muscle action potentials, whereas clindamycin had pronounced activity. Wright and Collier (1976b) have suggested that the local anaesthetic activity of clindamycin probably plays a major role in producing muscle paralysis and we have confirmed that the neuromuscular blocking action of clindamycin is similar to that of the local anaesthetic lignocaine.

Figure 5 shows a schematic representation of the potential sites of action of antibiotic drugs at the neuromuscular junction and surrounding areas, based on the present and previous data. It can be concluded that different antibiotics, often of the same chemical class, possess different mechanisms of action at the neuromuscular junction and hence caution is necessary when extrapolating data from a "typical" member of a class of antibiotics to any other antibiotic.

## ACKNOWLEDGEMENTS

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## REFERENCES

Brownlee, G. (1957). The actions of polymyxin E on the neuromuscular junction. *J. Physiol. (Lond)*, **136**, 19P.

Caputy, A. J., Kim, Y. I., and Sanders, D. B. (1981). The neuromuscular blocking effects of therapeutic concentrations of various antibiotics on normal rat skeletal muscle: a quantitative comparison. *J. Pharmacol. Exp. Ther.*, **217**, 369.

del Castillo, J., and Katz, B. (1954). Quantal components of the end-plate potential. *J. Physiol. (Lond.)*, 124, 560.

Diecke, F. P. J., Westecker, M. E., and Vogt, R. (1971). The effect of streptomycin on sodium and potassium currents in myelinated nerve. *Arch Int. Pharmacodyn. Ther.*, **193**, 5.

Dodge, D. A., and Rahamimoff, R. (1967). Cooperative action of calcium ions in transmitter release at the neuromuscular junction. *J. Physiol. (Lond.)*, 193, 419.

Dretchen, K. L., Gergis, S. D., Sokoll, M. D., and Long, J. P. (1972). Effects of various antibiotics on neuromuscular transmission. *Eur. J. Pharmacol.*, **18**, 201.

Durant, N. N., and Lambert, J. J. (1981). The action of polymyxin B at the frog neuromuscular junction. *Br. J. Pharmacol.*, **72**, 41.

Ellman, G. L., Courtney, K. D., Andres, V., and Featherstone, R. M. (1961). A new and rapid colorimetric determination of acetylcholinesterase activity. *Biochem. Pharmacol.*, **7**, 88.

Elmqvist, D., and Josefsson, J. D. (1962). The nature of the neuromuscular block produced by neomycine. *Acta Physiol. Scand.*, **54**, 105.

Fiekers, J. F. (1981). Neuromuscular block produced by polymyxin B: interaction with end-plate channels. *Eur. J. Pharmacol.*, **70**, 77.

—— Marshall, I. G., and Parsons, R. L. (1979). Clindamycin and lincomycin alter miniature endplate current decay. *Nature (Lond.)*, **281**, 680.

—— Parsons, R. L. (1980). Postsynaptic blockade by antibiotics: interaction with endplate channels. *Fed. Proc.*, **39**, 409.

Katz, B., and Thesleff, S. (1957). On the factors which determine the amplitude of the miniature end-plate potential. *J. Physiol. (Lond.)*, **137**, 267.

Lambert, J. J., Durant, N. N., Reynolds, L. S., Volle, R. L., and Henderson, E. G. (1981). Characterisation of end-plate conductance in transected frog muscle: modification by drugs. *J. Pharmacol. Exp. Ther.*, **216**, 62.

Lüllmann, H., and Reuter, H. (1960). Über die hemmung der neuromuskularen Übertragung durch einige. *Antibiotika Chemother.*, **1**, 375.

Maeno, T., and Enomoto, K. (1980). Reversal of streptomycin-induced blockade of neuromuscular transmission by 4-aminopyridine. *Proc. Japan Acad.*, **56B**, 486.

Manthey, A. A. (1966). The effects of calcium on the desensitization of membrane receptors at the neuromuscular junction. *J. Gen. Physiol.*, **49**, 963.

Martin, A. R. (1955). A further study of the statistical composition of the end-plate potential. *J. Physiol. (Lond.)*, **130**, 114.

Miyamoto, M. D. (1975). Binomial analysis of quantal transmitter release at glycerol treated frog neuromuscular junctions. *J. Physiol. (Lond.)*, **250**, 121.

Pennefather, P., and Quastel, D. M. J. (1980). Actions of anesthetics on the function of nicotinic acetylcholine receptors. *Prog. Anesthesiol.*, **2**, 45.

Pittinger, C. B., and Adamson, R. (1972). Antibiotic blockade of neuromuscular function. *Ann. Rev. Pharmacol.*, **12**, 169.

Prado, W. A., Corrado, A. P., and Marseillan, R. F. (1978). Competitive antagonism between calcium and antibiotics at the neuromuscular junction. *Arch. Int. Pharmacodyn. Ther.*, **281**, 297.

Rubbo, J. T., Gergis, S. D., and Sokoll, M. D. (1977). Comparative neuromuscular effects of lincomycin and clindamycin. *Anesth. Analg. (Cleve.)*, **56**, 329.

Sanders, W. E., and Sanders, C. C. (1979). Toxicity of antibacterial agents: mechanism of action on mammalian cells. *Ann. Rev. Pharmacol. Toxicol.*, **19**, 53.

Singh, Y. N., Harvey, A. L., and Marshall, I. G. (1978). Antibiotic-induced paralysis of the mouse phrenic nerve–hemidiaphragm preparation, and reversibility by calcium and by neostigmine. *Anesthesiology*, **48**, 418.

—— Marshall, I. G., and Harvey, A. L. (1978a). Some effects of the aminoglycoside antibiotic amikacin on neuromuscular and autonomic transmission. *Br. J. Anaesth.*, **50**, 109.

——————— (1978b). Reversal of antibiotic-induced muscle paralysis by 3, 4-diaminopyridine. *J. Pharm. Pharmacol.*, **30**, 249.

——————— (1979). Depression of transmitter release and postjunctional sensitivity during neuromuscular block produced by antibiotics. *Br. J. Anaesth.*, **51**, 1027.

——————— (1980). The mechanisms of the muscle paralysing actions of antibiotics and their interaction with neuromuscular blocking agents. *Rev. Drug Metab. Drug Interact.*, **3**, 129.

Sokoll, M. D., and Diecke, F. P. J. (1969). Some effects of streptomycin on frog nerve *in vitro*. *Arch. Int. Pharmacodyn. Ther.*, **177**, 332.

—— Gergis, S. D. (1981). Antibiotics and neuromuscular function. *Anesthesiology*, **55**, 148.

Wright, J. M., and Collier, B. (1976a). The site of the neuromuscular block produced by polymyxin B and rolitetracycline. *Can. J. Physiol. Pharmacol.*, **54**, 926.

————— (1976b). Characterisation of the neuromuscular block produced by clindamycin and lincomycin. *Can. J. Physiol. Pharmacol.*, **54**, 937.

Zar, J. H. (1974). *Biostatistical Analysis*. Englewood Cliffs, New Jersey: Prentice-Hall.

## EFFETS DE BLOCAGE PRE- ET POST-JONCTIONNELS DE DIVERS ANTIBIOTIQUES: AMINOSIDES, POLYMIXINE, TETRACYCLINE ET LINCOSAMIDE

### RESUME

Les effets de sept antibiotiques (streptomycine, amikacine, polymixine B, lincomycine, clindamycine, tétracycline et oxytetracycline) ont été comparés à ceux du magnésium, de la tubocurarine et de la lignocaïne sur une préparation de muscle de crapeau en utilisant des techniques d'enregistrement intracellulaires. Tous les composés, à l'exception de la tubocurarine, diminuaient le nombre de potentiels miniatures. Les effets presynaptiques du magnésium, de la streptomycine, de l'amikacine, de la polymyxine B et de l'oxytétracycline (mais pas des autres agents) étaient bien annulés en augmentant la concentration calcique. A des concentrations qui déprimaient le nombre de potentiels miniatures, seuls le magnésium, la tétracycline et l'oxytétracycline ne diminuaient pas la sensibilité post-synaptique. D'autres effets post-synaptiques des agents ont été révélés par des modifications du devenir en fonction du temps des potentiels post-synaptiques. Tous les agents testés, à l'exception du magnésium, de la tubocurarine et de la lincomycine, entrainaient des modifications des potentiels d'action musculaires. Aucun de ces composés n'avait d'activité anticholinestérasique. Les résultats confirment que l'aminoglycoside, la polymyxine, la tétracycline et la lincosamide entraînent un bloc neuromusculaire par une association d'actions à la fois pré- et post-synaptiques.

## PRÄ- UND POSTSYNAPTISCHE HEMMWIRKUNG DER AMINOGLYKOSIDE, VON POLYMYXIN, TETRAZYKLIN UND LINCOSAMIDANTIBIOTIKA

### ZUSAMMENFASSUNG

Die Wirkungen von sieben Antibiotika (Streptomycin, Amikacin, Poylymyxin B, Linkomycin, Klindamycin, Tetrazyklin und Oxytetrazyklin) wurden mit denen von Magnesium, Tubokurarin und Lidokain an einem N.-Sartorius Präparat aus dem Ischiasnerv des Frosches verglichen, indem man sich intrazellulärer Aufzeichnungstechniken bediente. Alle Mittel außer Tubokurarin setzten den Quanteninhalt der Endplattenpotentiale herab. Die präsynaptischen Wirkungen von Magnesium, Streptomycin, Amikacin, Polymixin B und Oxytetrazyklin (aber nicht die der anderen Mittel) wurde gut durch Erhöhung der Calzium-Konzentration aufgehoben. Bei Konzentrationen, die den Quanteninhalt herabsetzten, setzte nur Magnesium, Tetrazyklin und Oxytetrazyklin die postsynaptische Empfindlichkeit nicht herab. Weitere postsynaptische Wirkungen der Drogen zeigten sich durch Änderungen der Zeitverläufe der Endplattenpotentiale. Alle Mittel, außer Magnesium, Tubokurarin und Linkomycin riefen Veränderungen der Zeitverläufe der Endplattenpotentiale hervor. Keines der Mittel hatter eine anticholinesterase-Aktivität. Die Ergebnisse bekräftigen, daß Aminoglykoside, Polymixin, Tetrazykline und Lincosamid-Antibiotika die neuromuskuläre Blockade durch eine Kombination von sowohl prä- als auch postganglionären Wirkungen entfalten.

## EFECTOS DE BLOQUEO PRE- Y POST-JUNCIONAL DEL AMINOGLICOSIDO, DE LA POLIMIXINA, DE LA TETRACICLINA Y DE LOS ANTIBIOTICOS DE LINCOSAMIDO

### SUMARIO

Se llevó a cabo una comparación de los efectos de siete antibióticos (estreptomicina, amiquacina, polimixina B, lincomicina, clindamicina, tetraciclina y oxitetraciclina) con los del magnesio, de la tubocurarina y de la lignocaina en preparaciones músculo sartorio–nervio sciático de rana, mediante técnicas de registro intracelular. Todos los compuestos salvo la tubocurarina hicieron bajar el contenido cuántico del potencial de placa-terminal. Al aumentar la concentración de calcio, se invertieron bastante los efectos pre-juncionales del magnesio, de la estreptomicina, de la amiquacina, de la polimixina B y de la oxitetraciclina (pero, no fué así para las demás substancias). Con concentraciones que deprimían el contenido cuántico, sólo el magnesio, la tetraciclina y la oxitetraciclina no pudieron reducir la sensibilidad post-juncional. Las alteraciones de las trayectorias-tiempo de los potenciales de placa-terminal revelaron efectos post-juncionales adicionales de las drogas. Todas las substancias ensayadas salvo el magnesio, la tubocurarina y la lincomicina, provocaron cambios de los potenciales de acción del músculo. Ninguno de los compuestos tuvo alguna actividad anticolinesterasa. Los resultados permiten confirmar que los antibióticos de aminoglicosido, polimixina, tetraciclina y lincosamido producen un bloqueo neuromuscular mediante una combinación de las acciones pre- y post-juncionales.

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# *IN VITRO* COMPARISON BETWEEN THE NEUROMUSCULAR AND GANGLION BLOCKING POTENCY RATIOS OF ATRACURIUM AND TUBOCURARINE

T. E. J. HEALY AND J. P. PALMER

## SUMMARY

Results from *in vitro* experiments, using the hypogastric nerve – vas deferens preparation, and the phrenic nerve – hemidiaphragm preparation of the guineapig, have been used to determine the separation between the neuromuscular and ganglionic blocking effects of atracurium and tubocurarine. Regression lines were used to calculate the concentrations of each drug (99% confidence limits) which would produce a 50% blockade ($EC_{50}$) of ganglionic and neuromuscular transmission. The equipotent molar ratio, using $EC_{50}$ values, for ganglionic/neuromuscular blockade was 48 for atracurium and 9.4 for tubocurarine.

The tendency of drugs which produce neuromuscular blockade also to reduce ganglionic transmission is recognized. The ganglion blocking potency of tubocurarine and hexamethonium have been shown to be similar (Paton, 1959; Birmingham and Hussain, 1980) and furthermore tubocurarine may produce some ganglion blockade in a dose range similar to that required to produce neuromuscular block (Bowman, 1982). A ganglion blocking action may impair the autonomic reflexes occurring during surgical operations (Burstein et al., 1950) and this may be associated with hypotension (McDowell and Clark, 1969). The separation between the dose of drug which produces muscle relaxation and the dose which produces ganglion blockade is therefore an important consideration before the clinical introduction of a new muscle relaxant.

Atracurium, one of a new series of neuromuscular blocking drugs (Stenlake, 1979), has been reported to have a minimal effect on sympathetic mechanisms (Hughes and Chapple, 1981). However, the same authors suggest that, whilst indirect evidence indicated that histamine release was primarily responsible for the cardiovascular effects, a component of these effects may also be caused by sympathetic blockade.

It would therefore be instructive to examine the relative neuromuscular and ganglionic blocking potencies of atracurium and tubocurarine using isolated tissue preparations, from the same species, in which the effects of a range of drug concentrations may be compared.

## METHOD

The effects of atracurium or tubocurarine on neuromuscular and ganglion transmission were examined using the guineapig isolated phrenic nerve–diaphragm preparation and the guineapig isolated hypogastric nerve – vas deferens preparation respectively.

Guineapigs were killed by a blow on the head and bled from an incision in the throat.

### *The guineapig isolated phrenic nerve–diaphragm preparation*

The left phrenic nerve and hemidiaphragm were dissected from male or female guineapigs (600–800 g) as described for the rat by Bulbring (1946), and set up in an organ bath containing 50 ml of Krebs solution at 37 °C bubbled with 95% $O_2$ and 5% $CO_2$. A supramaximal rectangular wave stimulus of 0.2 ms pulse duration was applied to the nerve at a frequency of 0.1 Hz. The muscle contractions were detected with an isometric transducer and amplified and recorded on a Grass polygraph (multichannel model 7D). The preparation was allowed a settling period of at least thirty minutes before addition of the drug under test. During this period the preparation was washed at three minute intervals. At the end of the settling period baseline responses were recorded for three minutes, then drug was added. A contact time of four minutes was allowed after which the preparation was washed at least four times in

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drug-free Krebs solution, with three minute intervals between each wash, to re-establish the baseline response. The effects of eight drug concentrations were measured consecutively. Five guineapig preparations were used for each drug.

### *The guineapig isolated hypogastric nerve – vas deferens preparation*

The left hypogastric nerve, hypogastric plexus and vas deferens were dissected from a male guineapig (600–800 g) (Hukovic, 1963) and set up in a 50 ml bath of Krebs solution at 37 °C bubbled with 95% $O_2$ and 5% $CO_2$. Nerve and muscle were stimulated alternately using conventional bipolar platinum ring electrodes for the hypogastric nerve and parallel platinum wire electrodes for the post-ganglionic intramural nerve fibres in the vas deferens (Birmingham and Wilson, 1963). Supraximal rectangular wave stimuli were used (hypogastric nerve 40 V, intramural nerve fibres 110 V) of 0.2 ms pulse duration at a frequency of 20 Hz. Each stimulus was applied for 20 s, the time interval between stimuli being 2 min. Contraction of the vas (longitudinal shortening) was recorded using an isotonic transducer and Byrans chart recorder. The preparation was allowed a settling period of at least thirty minutes before addition of the first drug concentration. Drug was added immediately after a muscle contraction and allowed to act for a cycle of eight alternate nerve and muscle stimulations (total contact time 18 min 40 s). A cumulative dose–response curve was obtained by repeatedly doubling the concentration for each successive cycle of stimulations. The drug concentration was increased until complete blockade of the response to nerve stimulation was obtained. The effect of guanethidine $4 \times 10^{-4}$ mol litre$^{-1}$ on the response to post-ganglionic stimulation was then recorded. The bath fluid was then changed every three minutes until the contraction responses of the vas deferens to pre-ganglionic and post-ganglionic stimulation returned to their pre-drug level. Vasa deferentia from five guineapigs were used.

## DRUGS

The responses of the guineapig phrenic nerve – hemidiaphragm and the hypogastric nerve – vas deferens preparations were examined using either atracurium ($10^{-7}$ M – $1.28 \times 10^{-5}$ M and $10^{-6}$ M – $5.12 \times 10^{-4}$ M respectively) or tubocurarine ($10^{-7}$ M – $2.6 \times 10^{-5}$ M and $10^{-6}$ M – $1.28 \times 10^{-5}$ M respectively). These drug concentrations are expressed as moles of drug per litre of bath fluid. Assuming a total e.c.f. volume of 9 litre for a 60 kg man, $10^{-5}$ mol litre$^{-1}$ (12 μg ml$^{-1}$ atracurium, 0.7 μg ml$^{-1}$ tubocurarine) equates to a dosage of 1.86 mg kg$^{-1}$ (atracurium) and 1.04 mg kg$^{-1}$ (tubocurarine).

A $10^{-2}$ M stock solution of the dibesylate salt of atracurium was made in Krebs solution just prior to use and was acidified by the presence of $10^{-2}$ M ascorbic acid to avoid decomposition via the Hoffman route (Hughes and Chapple, 1981). In the bath fluid ascorbate was thus present in equimolar concentrations to the drug, and at those levels did not alter the physiological pH of the gassed Krebs solution. Guanethidine and tubocurarine were similarly treated (Drury, Birmingham and Healy, 1980). The composition of the Krebs solution is as follows (mmol litre$^{-1}$): NaCl 119, KCl 4.7, $MgSO_4$ 1.2, $NaH_2PO_4$ 0.9, $CaCl_2$ 2.5 and glucose 11.1.

## RESULTS

Both atracurium and tubocurarine reduce the contraction response of the diaphragm and the vas deferens to phrenic nerve and hypogastric nerve stimulation respectively. An example of the recordings obtained are shown in figures 1 and 2. The mean values for the contraction responses expressed as a percentage of the control values were plotted as a log concentration response curve shown in fig. 3. For each preparation regression analysis of the linear part of the curve allowed determination of the concentrations of drug which would produce a 50% blockade ($EC_{50}$). These values, together with the Pearson's product Moment Correlation Coefficients $R$, are shown in table I. The coefficient $R$ defines the degree of relation between the two variables log dose and response. A value of 0 indicates no systematic relation whilst a value of ±1 indicates a perfect correlation. Using statistical tables for the distribution of $R$ the results obtained were shown to lie within 99% confidence limits ($P = 0.01$).

Atracurium did not reduce the response to transmural (post-ganglionic) stimulation but in fact slightly enhanced it. The mean and SEM inhibition of the response to transmural stimulation was $-2.9\% \pm 0.61$.

Guanethidine ($4 \times 10^{-4}$ mol litre$^{-1}$) completely blocked the response of the vas deferens to transmural stimulation. However this blockade was reversed by changing the stimulation rate from 20 Hz to 0.2 m s$^{-1}$ (fast) to 1 Hz 100 m s$^{-1}$ (slow).

The separation between the neuromuscular and ganglionic blocking potencies of the two drugs was

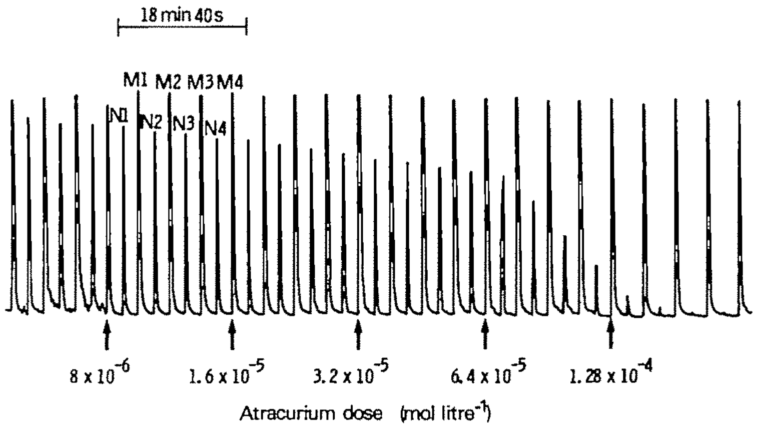

FIG. 1. The effect of increasing concentrations of atracurium on the contraction response of the vas deferens to preganglionic, hypogastric nerve, stimulation (N1, N2, N3, N4, etc.) and to post-ganglionic, intramural nerves, stimulation (M1, M2, M3, etc.).

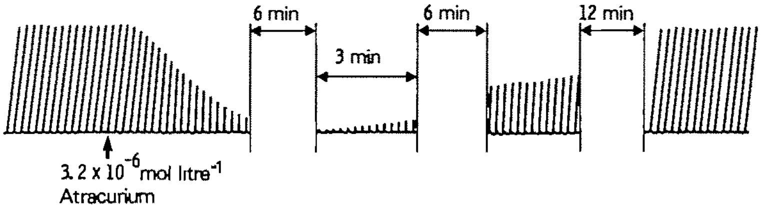

FIG. 2. The contraction response of the diaphragm to phrenic nerve stimulation and the blocking action of atracurium $3.2 \times 10^{-6}$ mol litre$^{-1}$ on the contraction response. The effect of three periods, two of 6 min and one of 12 min, of washout of drug are shown.

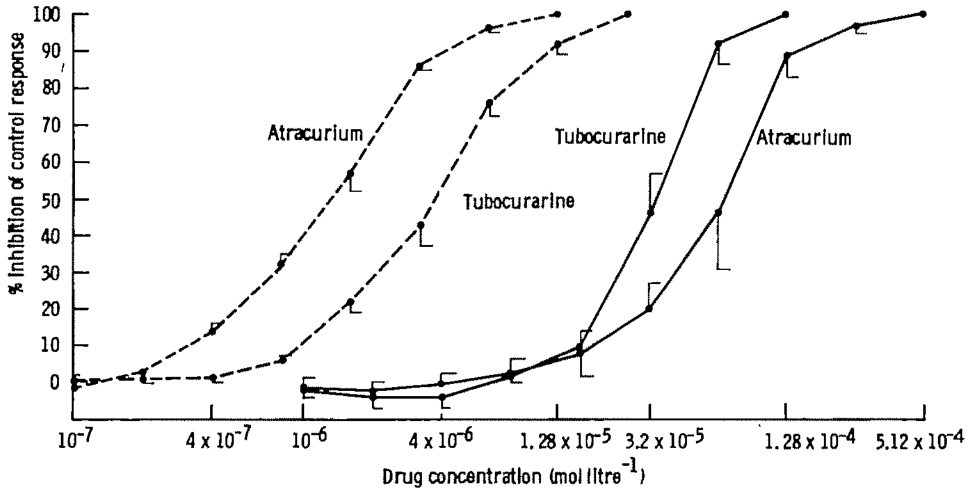

FIG. 3. Log dose–response curves for atracurium and for tubocurarine on the response of the diaphragm to phrenic nerve stimulation (—) and the response of the vas deferens to hypogastric nerve stimulation (———). The mean and standard error of the response for each concentration of drug tested are shown ($n = 5$).

determined from the ratio between the $EC_{50}$ values for ganglionic and neuromuscular blockade (equipotent molar ratio, EPMR). This separation was shown to be greater for atracurium than for tubocurarine, the values for EPMR being 48 and 9.4 respectively, see table I.

TABLE I. *Mean concentration (with 99% confidence limits) for 50% reduction of the response ($EC_{50}$) of the hemidiaphragm (NMB) and the vas deferens (GB).* EPMR = *Equipotent Molar Ratio i.e.* ($EC_{50}$ GB/$EC_{50}$ NMB). *R* = *Pearson's Product Moment Coefficient*

| | $EC_{50}$ | (mol litre$^{-1}$) | |
|---|---|---|---|
| Drug | NMB | GB | EPMR |
| Atracurium | $1.28 \times 10^{-6}$<br>$R = 0.967978$ | $6.15 \times 10^{-5}$<br>$R = 0.821636$ | 48.0 |
| Tubocurarine | $3.44 \times 10^{-6}$<br>$R = 0.938087$ | $3.24 \times 10^{-5}$<br>$R = 0.919568$ | 9.4 |

## DISCUSSION

The separation between neuromuscular and sympathetic ganglionic blockade is an important consideration in the assessment of the clinical value of a neuromuscular blocking drug and has been examined using *in vivo* techniques (Hughes and Chapple, 1976). However other factors such as histamine release, vagal blockade or compensatory mechanisms may disguise the magnitude of the sympathetic ganglionic blockade. These effects may be avoided by the use of isolated tissue preparations (Birmingham and Hussain, 1980). In the present study the separation between neuromuscular and ganglionic blockade has been examined using isolated tissues from the same species. The neurogenic identity of the post-ganglionic stimulation was validated by observing the reversal of the blockade induced by guanethidine by changing the transmural stimulus parameters (Bentley and Sabine, 1963; Birmingham and Wilson, 1963). The muscle does not respond to direct stimulation at high frequencies, and therefore contraction responses are associated with post-ganglionic nerve stimulation. However, guanethidine blocks the neuromuscular junction on the vas deferens and hence the response to nerve stimulation. The muscle will nonetheless contract if stimulated directly. This, however, requires the use of slower frequencies of stimulation.

Results of the $EC_{50}$ values for tubocurarine obtained in the present study are comparable to those obtained by Birmingham and Hussain (1980). For neuromuscular blockade $EC_{50}$ values ($10^{-6}$ mol litre$^{-1}$) were 3.44 and 6.7; for ganglion blockade they were 32.4 and 45 (present study quoted first).

Comparison of the EPMR values obtained in the present study and those reported for other muscle relaxants by Birmingham and Hussain (1980) suggest that, in the separation of neuromuscular and ganglionic blockade, atracurium is second only to pancuronium and five times that of tubocurarine. The EPMR values are as follows: atracurium 48 (present study); tubocurarine 9.4 (present study); tubocurarine 6.7; pancuronium 200; gallamine 24.3; alcuronium 22.9 and fazadinium 2.3 (Birmingham and Hussain, 1980).

Hughes and Chapple (1981) used *in vivo* studies to assess the degree of separation between neuromuscular, sympathetic and vagal blockade. Their results suggested that atracurium is unlikely to have more than a negligible effect on ganglionic transmission at concentrations required to produce a neuromuscular block. Their EPMR values for neuromuscular/vagal blockade were: atracurium 24.4, tubocurarine 1.5.

The effect of atracurium on the sympathetic system was also examined by Hughes and Chapple (1981) using *in vivo* techniques. In experiments performed using cats and monkeys they found that significant hypotension was evident at a dose 16 times greater than that required for full neuromuscular blockade (4 mg kg$^{-1}$), although in dogs 2 mg kg$^{-1}$ reduced mean arterial pressure to 53 ± 20.2% of the control value, and this latter finding agrees closely with the results presented here. Nonetheless, it would appear that a high degree of separation between the dose of atracurium required to produce neuromuscular blockade and the dose required to produce sympathetic ganglion blockade is suggested with *in vivo* and *in vitro* studies.

Although it must be remembered that results, obtained by the use of *in vivo* and *in vitro* animal studies, may not be identical with those obtained in clinical practice, *in vitro* studies allow the study of drugs under standard conditions and enable a prediction of their relative effects at separate sites. From these results it is suggested that the use of atracurium is much less likely than tubocurarine to be associated with sympathetic blockade.

### REFERENCES

Bentley, G. A. and Sabine, J. R. (1963). The effects of ganglion-blocking and postganglionic sympatholytic drugs on preparations of the guineapig vas deferens. *Br. J. Pharmacol.*, **21**, 190.

Birmingham, A. T. and Hussain, S. Z. (1980). A comparison of the skeletal neuromuscular and autonomic ganglion-blocking potencies of five non depolarizing relaxants. *Br. J. Pharmacol.*, **70**, 501.

—— Wilson, A. B. (1963). Preganglionic and postganglionic stimulation of the guineapig isolated vas deferens preparation. *Br. J. Pharmacol.*, **21**, 569.

Bowman, W. C. (1982). Non-relaxant properties of neuromuscular blocking drugs. *Br. J. Anaesth.*, **54**, 147.

Bülbring, E. (1946). Observations on the phrenic nerve diaphragm preparation of the rat. *Br. J. Pharmacol.*, **38**, 61.

Burstein, C. L., Jackson, A., Bishop, H. F. and Rovenstine, E. A. (1950). Curare in the management of autonomic reflexes. *Anesthesiology*, **11**, 409.

Drury, P. J., Birmingham, A. T. and Healy, T. E. J. (1980). The effect of ascorbic acid on the interaction of adrenaline and neostigmine on neuromuscular transmission. *J. Pharmac. Meth.*, **4**, 89.

Hughes, R. and Chapple, D. J. (1976). Effects of non-depolarizing neuromuscular blocking agents on peripheral and autonomic mechanisms in cats. *Br. J. Anaesth.*, **48**, 59.

—— —— (1981). The pharmacology of atracurium: A new competitive neuromuscular blocking agent. *Br. J. Anaesth.*, **53**, 31.

Hukovic, S. (1961). Responses of the isolated sympathetic nerve ductus deferens preparation of the guineapig. *Br. J. Pharmacol.*, **16**, 188.

McDowell, S. A. and Clarke, R. S. J. (1969). A clinical comparison of pancuronium with d-tubocurarine. *Anaesthesia*, **24**, 581.

Paton, W. D. M. (1959). The effects of muscle relaxants other than muscle relaxation. *Anesthesiology*, **20**, 453.

Stenlake, J. B. (1979). Ions-cyclic nucleotids-cholinergy; in *Advances in Pharmacology and Therapeutics* (ed. J. C. Stoclet), p. 303. Oxford and New York: Pergamon Press.

## COMPARAISON *IN VITRO* ENTRE LES CAPACITES DE BLOCAGE RELATIVES NEUROMUSCULAIRES ET GANGLIONNAIRES DE L'ATRACURIUM ET DE LA TUBOCURARINE

### RESUME

Les résultas d'experiences *in vitro*, utilisant des préparations de nerf hypogastrique–canal déférent et de nerf phrénique–hémidiaphragme chez le cobaye, ont été utilisés pour préciser la limite entre les effets ganglioplégiques et les effets de bloc neuromusculaire de l'atracurium et de la tubocurarine. Des courbes de régression ont été utilisées pour calculer les concentrations de chaque agent (intervalles de confiance 99%) qui permettraient d'obtenir un bloc de 50% ($EC_{50}$) de la transmission ganglionnaire et neuromusculaire. Le rapport molaire équipotent était, en utilisant les valeurs des $EC_{50}$, de 48 pour le bloc ganglionnaire/neuromusculaire avec l'atracurium et de 9,4 avec la tubocurarine.

## *IN VITRO* VERGLEICH ZWISCHEN NEUROMUSKULÄRER UND GANGLIENBLOCKENDER POTENZ VON ATRAKURIUM UND TUBOCURARIN

### ZUSAMMENFASSUNG

Die Ergebnisse von *in vitro* Experimenten, die an einem Präparat aus N. Hypogastricus – vas deferens und einem Präparat aus N. Phrenikus – Zwerchfellhälfte vom Meerschweinchen gewonnen wurden, dienten dazu, die Trennung zwischen neuromuskulärer und ganglienblockender Wirkung von Atrakurium und Tubokurarin zu bestimmen. Zur Berechnung der Konzentrationen, die von jedem Mittel notwendig waren (99% Vertrauensbereich), um eine 50% Blockade ($EC_{50}$) der ganglionären und neuromuskulären Ubertragung zu erreichen, wurden Regressionskurven benützt. Die äquipotente molare Verhältniszahl für die ganglionäre/neuromuskuläre Blockade (unter Benützung von $EC_{50}$ Werten) war 48 für Atrakurium und 9,4 für Tubokurarin.

## COMPARACIÓN *IN VITRO* ENTRE LAS RELACIONES DE POTENCIA BLOQUEADORA NEUROMUSCULAR Y GANGLIONAR DEL ATRACURIO Y DE DE LA TUBOCURARINA

### SUMARIO

Se usaron los resultados de experimentos *in vitro* en base a la preparación de vas deferens–nervio hipogástrico y de la preparación hemidiafragma–nervio frénico de cochinos de la India para determinar la separación entre los efectos bloqueadores ganglionares y neuromusculares del atracurio y de la tubocurarina. Se emplearon las líneas de regresión para calcular las concentraciones de cada substancia (límites de confianza del 99%) que pudieran provocar un bloqueo al 50% ($EC_{50}$) de la transmisión ganglionar y neuromuscular. La relación molar equipotente, al usar valores $EC_{50}$, en lo que se refiere al bloqueo ganglionar/neuromuscular fue del 48 para el atracurio y del 9,4 para la tubocurarina.

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# METABOLISM OF MONOAMINES IN MALIGNANT HYPERTHERMIA-SUSCEPTIBLE PIGS

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## SUMMARY

A comparison of the monoamine oxidase activities in the hypothalamus and striatum between malignant hyperthermia-susceptible (Pietrain) and malignant hyperthermia-resistant (Landrace/Large White) pigs showed no significant difference between the two breeds. The concentrations of noradrenaline, dopamine and their non-O-methylated metabolites did not reflect the low activities of monoamine oxidase type A differentially. The malignant hyperthermia-susceptible pigs had significantly greater concentrations of 3,4-dihydroxyphenyl glycol in the striatum, and of 3,4-dihydroxymandelic acid in the hypothalamus. Consequently, in the brain, low monoamine oxidase type A activity does not appear to be involved in susceptibility to malignant hyperthermia. In addition, monoamine oxidase activities in the heart, liver, kidney and intestinal mucosa and catechol-O-methyl transferase activities in the kidney were the same in the susceptible and resistant pigs.

Susceptibility to malignant hyperthermia in pigs is defined by the onset of malignant hyperthermia in response to the administration of halothane or suxamethonium (Hall et al., 1966; Harrison et al., 1968). Porcine malignant hyperthermia is symptomatically and physiologically very similar to malignant hyperthermia in man (for reviews, see Lucke, Hall and Lister, 1979; Gronert, 1980). Malignant hyperthermia is characterized by a progressive increase in body temperature, severe muscular rigidity and metabolic acidosis. In malignant hyperthermia-susceptible pigs, a malignant hyperthermia-like response called the Porcine Stress Syndrome can be initiated by stress alone (Briskey, 1964).

An involvement of the sympathetic nervous system in malignant hyperthermia and the Porcine Stress Syndrome is indicated by an increase in circulating concentrations of noradrenaline and adrenaline, although data on the effects of drugs affecting adrenergic function are conflicting (for reviews see Williams, 1976; Lucke, Hall and Lister, 1979; Gronert, 1980). Debate in this area centres around whether the sympathetic nervous system plays a primary or secondary role (Gronert, Milde and Theye, 1977; Lucke et al., 1978). It is difficult to assess the possible role of the sympathetic nervous system in malignant hyperthermia-susceptible pigs or in the Porcine Stress Syndrome when most studies are carried out on precipitating the syndrome with halothane or suxamethonium chloride—drugs which directly affect ion movements in muscle and nervous tissue.

Two enzymes are responsible for the degradation of catecholamines: the flavin-containing enzyme monoamine oxidase (MAO, monoamine $O_2$: oxidoreductase, EC 1.4.3.4.) and catechol-O-methyl transferase (COMT, EC 2.1.1.6.). Monoamine oxidase appears to exist in two forms, termed MAO-A and MAO-B. The A and B forms of this enzyme have different substrate specificities and inhibitor sensitivities (for review see Fowler et al., 1978). In most theories, MAO-A is responsible for the deamination of 5-hydroxytryptamine and noradrenaline, and MAO-B for the deamination of $\beta$-phenethylamine. Both forms of the enzyme metabolize tyramine and dopamine (for review see Tipton, Houslay and Mantle, 1976). The pathways of metabolism of dopamine and noradrenaline are

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shown in figure 1. The activity of COMT represents an alternative means of inactivating the catecholamines by catalysing the formation of their *m*-O-methyl derivatives which are then metabolized by the same pathway as the non-methylated amines. In the rat and human brain, monoamine oxidase is present in excess, so small fluctuations in enzyme concentrations induced by age, neurone loss, etc., do not significantly alter the concentrations of central catecholamines (Green and Grahame-Smith, 1978). However, in the pig, there is little, if any, MAO-A present (Hall, Logan and Parsons, 1969; Tipton, 1971; Squires, 1972; Stanton et al., 1975), thus raising the possibility that a decreased deamination of noradrenaline may play a role in the Porcine Stress Syndrome and susceptibility to malignant hyperthermia. The experiments described here were designed to test this hypothesis.

## MATERIALS

Normetanephrine (NM) hydrochloride, noradrenaline (NA) hydrochloride, 4-hydroxy-3-methoxymandelic acid (VMA), bis (3-methoxy-4-hydroxyphenyl glycol (MHPG) piperazine, 3-methoxytyramine (3MT) hydrochloride, 4-hydroxy-3-methoxyphenyl acetic acid (HVA), ethylene glycol-bis (β-amino ethyl ether) N,N′-tetra acetic acid (EGTA), bovine serum albumin (fraction V) and 2-phenylethylamine hydrochloride were supplied by Sigma (London) Chemical Co. Ltd. 3,4-Dihydroxyphenyl acetic acid (DOPAC), 3,4-dihydroxyphenyl glycol (DHPG) and 3,4-dihydroxymandelic acid (DHMA) were from Calbiochem, San Diego, California, U.S.A.; 3,4-dihydroxyphenethanol (DHPET) from Regis Chemical Co. and 5-hydroxytryptamine (5HT) creatinine sulphate was supplied by Koch Light Laboratories Ltd, Colnbrook, Bucks, England. S-Adenosyl [$^3$H]-methionine, 5-hydroxy [side chain-2-$^{14}$C]-tryptamine creatinine sulphate, tyramine-[7-$^{14}$C]-hydrochloride and 2-phenyl [1-$^{14}$C]-ethylamine hydrochloride were obtained from the Radiochemical Centre, Amersham, U.K. All other reagents were of ANALAR grade and supplied by BDH Chemicals Ltd, Poole, Dorset, U.K.

## METHODS

### *Animals*

In this study, four malignant hyperthermia-susceptible (Pietrain) pigs were compared with four malignant hyperthermia-resistant (Landrace/Large White) pigs. The malignant hyperthermia-susceptible pigs were identified by a screening test which involved exposure of the animal to halothane, in the manner described by Ahern and others (1980), at least 1 month before experimentation.

### *Dissection*

The animals were anaesthetized with sodium pentobarbitone (Sagatal, May and Baker, U.K.) as described by Ahern and others (1980). Anaesthesia was maintained for 1 h to stabilize the preparation before craniotomy was performed. The dissection procedure for removing the striatum and hypothalamus was based on the method described by Bardsley and Bachelard (1981a). The brain regions were frozen in liquid nitrogen and stored at −20 °C until analysis. Samples of liver, kidney, intestinal mucosa and heart were removed as rapidly as possible, postmortem. These tissues and the cere-

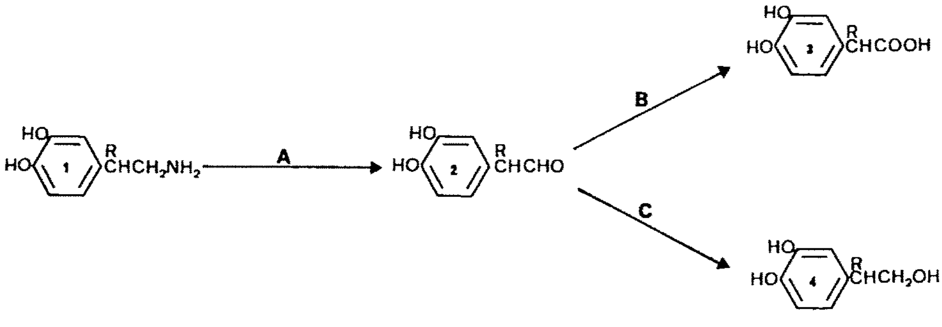

FIG. 1. The metabolism of dopamine and noradrenaline. The enzymes involved are: A = monoamine oxidase; B = aldehyde dehydrogenase; C = aldehyde reductase. The metabolites are, for R = H, 1: dopamine; 2: 3,4-dihydroxyphenylacetaldehyde; 3: 3,4-dihydroxyphenylacetic acid (DOPAC); 4: 3,4-dihydroxyphenethanol (DHPET); for R = OH, 1: noradrenaline; 2: 3,4-dihydroxyphenyl glycolaldehyde; 3: 3,4-dihydroxymandelic acid (DHMA); 4: 3,4-dihydroxyphenyl glycol (DHPG).

bral cortex were homogenized immediately, on ice, in phosphate buffer, and stored at −20 °C until analysis.

### *Assay of noradrenaline, dopamine and their non-O-methylated metabolites*

The concentrations of noradrenaline (NA), dopamine (DA), 3,4-dihydroxymandelic acid (DHMA), 3,4-dihydroxyphenyl glycol (DHPG), 3,4-dihydroxyphenyl acetic acid (DOPAC) and 3,4-dihydroxyphenethanol (DHPET) were determined radio-enzymatically by the method of Bardsley and Bachelard (1981b). External and internal standard curves were used to measure the recovery of each catecholamine. All measurements were carried out in duplicate.

### *Monoamine oxidase*

Monoamine oxidase activity towards 5-hydroxytryptamine (5HT) and $\beta$-phenethylamine (PEA) was measured by the method of Otsuka and Kobayashi (1964) as modified by Fowler and Tipton (1981). Aliquots of striatum and hypothalamus were incubated at 30 °C for 15 min to determine enzyme activity. For the other samples, activities were measured over three time-points at 37 °C.

### *Catechol-O-methyl transferase*

Catechol-O-methyl transferase activity was measured at three time-points (3, 6 and 9 min) at 37 °C in the pig kidney sample by the method of Gulliver and Tipton (1978). 3,4-Dihydroxyphenyl acetic acid, at a concentration of 3.0 mmol litre$^{-1}$, was used as the substrate.

### *Protein*

Protein was determined by the Biuret method (Gornall, Bardawill and David, 1949) or by the method of Markwell and others (1978).

## RESULTS AND DISCUSSION

The hypothalamus and striatum were chosen for the initial experiments because of their relatively high catecholamine concentrations and physiological roles. The hypothalamus is involved in the control of hormonal release from the pituitary, including stress-related hormones such as adrenocorticotrophic hormone. The striatum is intimately associated with muscular movement.

The concentrations of NA, DA, DHMA, DHPG, DOPAC and DHPET in the hypothalamus and striatum (table I) show that DHMA concentrations were significantly greater in the hypothalamus ($P < 0.025$) and that DHPG was significantly greater in the striatum ($P < 0.005$) from the malignant hyperthermia-susceptible pigs. The standard curves showing product formation with substrate concentration were linear over the range of substrate concentrations in the tissues.

Since NA is preferentially oxidized by monoamine oxidase type-A and DA is a substrate for both forms of the enzyme in most tissues (Tipton,

TABLE I. *Concentrations of noradrenaline (NA), dopamine (DA), DHMA, DOPAC, DHPG and DHPET in ng/mg protein (mean ± SD) in the hypothalamus and striatum from stress-susceptible and stress-resistant pigs* (n = *4*). *$P < 0.025$; †$P < 0.005$

| | Stress-resistant | | Stress-susceptible | |
|---|---|---|---|---|
| | Hypothalamus | Striatum | Hypothalamus | Striatum |
| Metabolite | | | | |
| DA | 1.27 ± 0.34 | 5.34 ± 3.71 | 3.20 ± 2.81 | 10.76 ± 0.19 |
| NA | 5.42 ± 0.24 | 1.70 ± 0.27 | 7.63 ± 3.18 | 2.13 ± 0.35 |
| DHMA | 0.14 ± 0.03 | 0.42 ± 0.35 | 0.33 ± 0.14* | 0.62 ± 0.37 |
| DOPAC | 0.69 ± 0.18 | 2.30 ± 1.92 | 2.28 ± 3.06 | 5.77 ± 3.16 |
| DHPG | 0.19 ± 0.07 | 0.10 ± 0.04 | 0.31 ± 0.12 | 0.24 ± 0.05† |
| DHPET | 0.24 ± 0.09 | 1.41 ± 0.81 | 1.74 ± 2.40 | 2.57 ± 1.17 |
| Ratios | | | | |
| DA/NA | 0.235 ± 0.063 | 3.033 ± 1.910 | 0.378 ± 0.151 | 4.627 ± 0.045 |
| $\frac{\text{DOPAC} + \text{DHPET}}{\text{DHMA} + \text{DHPG}}$ | 2.967 ± 0.823 | 7.539 ± 1.972 | 5.551 ± 5.668 | 9.534 ± 0.954 |

TABLE II. *Monoamine oxidase activity (pmol min$^{-1}$ per mg protein (mean ± SD) towards 5-hydroxytryptamine (5-HT) and β-phenethylamine (PEA) in the hypothalamus and striatum from malignant hyperthermia-susceptible and -resistant pigs* (n = 4)

| | MH-resistant | | MH-susceptible | |
|---|---|---|---|---|
| Substrate | Hypothalamus | Striatum | Hypothalamus | Striatum |
| 5-HT<br>0.2 mmol litre$^{-1}$ | 23 ± 10 | 24 ± 4 | 22 ± 7 | 22 ± 3 |
| PEA<br>0.05 mmol litre$^{-1}$ | 180 ± 40 | 270 ± 94 | 156 ± 33 | 219 ± 39 |

Houslay and Mantle, 1976), lack of monoamine oxidase type-A would be expected to result in smaller concentrations of DHMA and DHPG when compared with DOPAC and DHPET. This, however, was not found to be the case (see table I). Increased concentrations of the deaminated metabolites of NA were found in the malignant hyperthermia-susceptible pigs. These differences may be involved in the genesis of malignant hyperthermia, but it is also possible that they are the result of an unrelated strain difference. In addition, it should be noted that steady-state concentrations of deaminated metabolites may not be simply related to neuronal function.

Monoamine oxidase activity towards β-phenethylamine and 5-hydroxytryptamine (table II) shows that there is no significant difference between the activities in malignant hyperthermia-susceptible and malignant hyperthermia-resistant pigs.

The lack of difference in monoamine oxidase activities in the hypothalamus and striatum was also found, with 5-hydroxytryptamine, tyramine and β-phenethylamine as substrates in the cerebral cortex, heart, liver, kidney and intestinal mucosa (table III).

A recent paper has indicated that platelet monoamine oxidase in malignant hyperthermia-susceptible and -resistant pigs is the same (Dantzer and Hatey, 1981), although stress, induced by a variety of means, has been shown to result in increased monoamine oxidase activity in human platelets (Gawel et al., 1977; Matthew et al., 1981; Owen et al., 1977).

The ratio of 5-HT to β-phenethylamine activity is lower in the striatum and hypothalamus (table II) than in the cortex (table III). This is in agreement with the finding in the human brain that the relative activities of MAO-B : MAO-A are lowest in the cortical areas (Fowler and Oreland, 1981).

The activities of catechol-O-methyl transferase in the pig kidney were the same (222 ± 34 and 274 ± 82 pmol min$^{-1}$ per mg protein for the Landrace/Large White and Pietrain pigs respectively (means ± SD).

TABLE III. *Monoamine oxidase activities (pmol min$^{-1}$ per mg protein (mean ± SD)) towards 5-hydroxytryptamine (5-HT), tyramine (TYR) and β-phenethylamine (PEA) in various tissues from malignant hyperthermia-susceptible and malignant hyperthermia-resistant pigs (n = 4). Substrate concentrations were: 5-HT 0.2 mmol litre$^{-1}$; TYR 0.2 mmol litre$^{-1}$; PEA 0.05 mmol litre$^{-1}$*

| Tissue and substrate | MH-resistant | MH-susceptible |
|---|---|---|
| Brain | | |
| 5-HT | 260 ± 120 | 260 ± 120 |
| TYR | 760 ± 200 | 910 ± 280 |
| PEA | 660 ± 220 | 770 ± 300 |
| Liver | | |
| 5-HT | 310 ± 200 | 330 ± 140 |
| TYR | 480 ± 100 | 430 ± 120 |
| PEA | 830 ± 240 | 860 ± 540 |
| Kidney | | |
| 5-HT | 1220 ± 200 | 1570 ± 240 |
| TYR | 2490 ± 680 | 2660 ± 1000 |
| PEA | 2300 ± 400 | 2680 ± 420 |
| Intestine | | |
| 5-HT | 240 ± 140 | 220 ± 180 |
| TYR | 420 ± 240 | 520 ± 320 |
| PEA | 310 ± 220 | 330 ± 180 |
| Heart | | |
| 5-HT | 10 ± 4 | 13 ± 10 |
| TYR | 79 ± 28 | 75 ± 12 |
| PEA | 108 ± 66 | 125 ± 73 |

In summary, the experiments show that small concentrations, or lack of monoamine oxidase type-A do not appear to be involved in the genesis of malignant hyperthermia or the Porcine Stress Syndrome.

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## REFERENCES

Ahern, C. P., Somers, C. J., Wilson, P., and McLoughlin, J. V. (1980). Halothane-induced malignant hyperthermia: creatine phosphate concentration as an early indicator of the onset of the syndrome. *J. Comp. Pathol.*, **90**, 177.

Bardsley, M. E., and Bachelard, H. S. (1981a). Catecholamine levels and tyrosine hydroxylase activities in rat brain regions after chronic treatment with, and withdrawal of, methamphetamine. *Biochem. Pharmacol.*, **30**, 1543.

———— (1981b). Radioenzymatic assay for the simultaneous measurement of noradrenaline, dopamine and their non-O-methylated metabolites. *Cell. Mol. Biol.*, **27**, 71.

Briskey, E. J. (1964). Etiological status and associated studies of pale, soft, exudative porcine musculature. *Adv. Food Res.*, **13**, 89.

Dantzer, R., and Hatey, F. (1981). Plasma dopamine-beta-hydroxylase and platelet monoamine oxidase activities in pigs with different susceptibility to the malignant hyperthermia syndrome induced by halothane. *Reprod. Nutr. Dévelop.*, **21**, 103.

Fowler, C. J., Callingham, B. A., Mantle, T. J., and Tipton, K. F. (1978). Monoamine oxidase A and B: a useful concept. *Biochem. Pharmacol.*, **27**, 97.

——Oreland, L. (1981). Substrate and stereoselective inhibition of human brain monoamine oxidase by 4-dimethyl-α, 2-dimethylphenethylamine (FLA 336). *J. Pharm. Pharmacol.*, **33**, 403.

——Tipton, K. F. (1981). Concentration dependence of the oxidation of tyramine by the two forms of rat liver mitochondrial monoamine oxidase. *Biochem. Pharmacol.*, **30**, 3329.

Gawel, M., Glover, V., Park, D., Rose, F. C., and Sandler, M. (1977). The effect of exercise upon platelet MAO-B activity. *Clin. Sci. Molec. Med.*, **52**, 32P.

Gornall, A. G., Bardawill, C. J., and David, M. M. (1949). Determination of serum proteins by means of the biuret reaction. *J. Biol. Chem.*, **177**, 751.

Green, A. R., and Grahame-Smith, D. G. (1978). Processes regulating the functional activity of brain-5-hydroxytryptamine: results of animal experimentation and their relevance to the understanding and treatment of depression. *Pharmakopsychiatr.*, **11**, 3.

Gronert, G. A. (1980). Malignant hyperthermia. *Anesthesiology*, **53**, 395.

——Milde, J. H., and Theye, R. A. (1977). Role of sympathetic activity in porcine malignant hyperthermia. *Anesthesiology*, **47**, 411.

Gulliver, P. A., and Tipton, K. F. (1978). Direct extraction radioassay for catechol-O-methyl transferase activity. *Biochem. Pharmacol.*, **27**, 773.

Hall, D. W. R., Logan, B. W., and Parsons, G. H. (1969). Further studies on the inhibition of monoamine oxidase by M & B 9302 (clorgyline)-1. *Biochem. Pharmacol.*, **18**, 1447.

Hall, L. W., Woolf, N., Bradley, J. W. P., and Jolly, D. W. (1966). Unusual reaction to suxamethonium chloride. *Br. Med. J.*, **2**, 1305.

Harrison, G. G., Biebuyck, J. F., Terblanche, J., Dent, D. M., Hickman, R., and Saunders, S. J. (1968). Hyperpyrexia during anaesthesia. *Br. Med. J.*, **3**, 594.

Lucke, J. N., Denny, H., Hall, G. M., Lovell, R., and Lister, D. (1978). Porcine malignant hyperthermia VI: the effects of bilateral adrenalectomy and pretreatment with bretylium on the halothane-induced response. *Br. J. Anaesth.*, **50**, 241.

——Hall, G. M., and Lister, D. (1979). Malignant hyperthermia and the role of stress. *Ann. N.Y. Acad. Sci.*, **317**, 326.

Markwell, M. A. K., Hass, S. M., Bieber, L. L., and Tolbert, N. E. (1978). A modification of the Lowry procedure to simplify protein determination in membrane and lipoprotein samples. *Anal. Biochem.*, **87**, 206.

Matthew, R. J., Ho, B. T., Kralik, P., Taylor, D. L., and Claghorn, J. L. (1981). Catecholamines and monoamine oxidase in anxiety. *Acta Psychiatr. Scand.*, **63**, 245.

Otsuka, S., and Kobayashi, Y. (1964). A radioisotopic assay for monoamine oxidase determinations in human plasma. *Bicohem. Pharmacol.*, **13**, 995.

Owen, F., Acker, W., Bourne, R. C., Frith, C. D., and Riley, F. J. (1977). The effect on human monoamine oxidase activity of subcutaneous injection of adrenaline. *Biochem. Pharmacol.*, **26**, 2065.

Squires, R. F. (1972). Multiple forms of monoamine oxidase in intact mitochondria as characterised by selective inhibitors and thermal stability. A comparison of eight mammalian species. *Adv. Biochem. Psychopharmacol.*, **5**, 355.

Stanton, H. C., Cornejo, R. A., Mersmann, H. J., Brown, L. J., and Mueller, R. L. (1975). Ontogenesis of monoamine oxidase and catechol-O-methyl transferase in various tissues of domestic swine. *Arch. Int. Pharmacodyn. Ther.*, **213**, 128.

Tipton, K. F. (1971). Monoamine oxidases and their inhibitors; in *Mechanisms of Toxicity* (ed. W. N. Aldrich), p. 13. London: Macmillan Press.

——Houslay, M. D., and Mantle, T. J. (1976). The nature and location of the multiple forms of monoamine oxidase. *Ciba Found. Symp.*, **39**, 5.

Williams, C. H. (1976). Some observations on the etiology of the fulminant hyperthermia-stress syndrome. *Perspect. Biol. Med.*, **20**, 120.

## METABOLISME DES MONOAMINES CHEZ DES PORCS PREDISPOSES A L'HYPERTHERMIE MALIGNE

### RESUME

La comparaison des activités de la monamine oxydase dans l'hypothalamus et dans la striatum entre des porcs prédisposés à l'hyperthermie maligne (Pietrain) et des porcs résistants à celle-ci (Landrace/Large white) n'a pas montré de différence significative entre ces deux races. Les concentrations de noradrénaline, de dopamine et de leurs métabolites non-0-méthylés ne reflètaient pas de différences entre les faibles concentrations de monoamine oxydase de type A. Les porcs prédisposés à l'hyperthermie maligne avaient des concentrations significativement plus élevées de 3–4–di–OH-phénylglycol dans le striatum et d'acide 3–4–di–OH mandélique dans l'hypothalamus. En conséquence, dans le cerveau, de petites concentrations de monoamine oxydase de type A ne semblent pas impliquées dans la prédisposition à l'hyperthermie maligne. De plus, les activités de la monoamine oxydase dans le coeur, le foie, le rein et la muqueuse intestinale et les activitiés de la catéchol-0-méthyl transferase dans le rein sont les mêmes chez les porcs prédisposés et chez les autres.

## DER METABOLISMUS DER MONOAMINE BEI FÜR MALIGNE HYPERTHERMIE EMPFINDLICHEN SCHWEINEN

### ZUSAMMENFASSUNG

Ein vergleich der Monoamin-Oxidase-Aktivitäten in Hypothalamus und Striatum zwischen für maligne Hyperthermie empfindlichen (Pietrain) und gegen Maligne Hyperthermie resistenten (Landrasse/schwarz weiss) Schweinen zeigte keinen signifikanten Unterschied zwischen den beiden Rassen. Die Konzentrationen von Noradrenalin, Dopamin und ihren nicht-O-methylierten Metaboliten spiegelten nicht die geringen Unterschiede der Konzentrationen von Monoaminoxidase Typ A wieder. Die für Maligne Hyperthermie empfindlichen Schweine hatten signifikant höhere Konzentrationen von 3,4-dihydroxyphenylglycol im Striatum und von 3,4-dihydroxymandelsäure im Hypothalamus. Folglich scheinen im Gehirn geringe Konzentrationen von Monoaminoxidase Typ A nicht mit Empfindlichkeit auf Maligne Hyperthermie zusammen zu hängen. Zusätzlich waren die Monoaminoxidase Aktivitäten in Herz, Leber, Nieren und Darmschleimhaut und die Katechol-O-methyltransferase Aktivitäten in der Niere bei empfindlichen und resistenten Schweinen gleich.

## METABOLISMO DE LAS MONOAMINAS EN CERDOS EXPUESTOS A HIPERTHERMIA MALIGNA

### SUMARIO

En base a una comparación de las actividades de oxidasa de las monoaminas en el hipotálamo y el estriato entre cerdos susceptibles a hipertermia maligna (Piétrain) y cerdos resistantes a la hipertermia maligna (Landrace/Large White), no se demostró ninguna diferencia significativa entre las dos razas. Las concentraciones de noradrenalina, dopamina y sus metabólitos no-O-metilados no reflejaron de manera diferencial las pequeñas concentraciones de oxidasa de monoamina de tipo A. Los cerdos susceptibles a hipertermia maligna tenían concentraciones mayormente más elevadas de glicol dihidroxifenil-3,4 en el estriato y de ácido dihidroximandélico-3,4 en el hipotálamo. En consecuencia, las pequeñas concentraciones en el cerebro de oxidasa de monoamina de tipo A no parecen tener relación con la susceptibilidad a la hipertermia maligna. Además, las actividades de la oxidasa de monoamina en el corazón, el hígado, los riñones y la mucosa intestinal así como las actividades de la transferasa de metil-O-catecol en los riñones eran iguales en los cerdos susceptibles como en los cerdos resistantes.

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# SOME CAPABILITIES AND LIMITATIONS OF MULTIPLE REGRESSION ANALYSIS: APPLICATION TO CANINE CORONARY BLOOD FLOW

A. M. S. BLACK AND P. FOËX

## SUMMARY

Changes in inspired oxygen and carbon dioxide concentration produced concurrent changes in systemic and coronary haemodynamics in 39 anaesthetized dogs. These changes provided the data base for an exercise in multiple regression analysis using SPSS packages. The physiological problem was to identify influences on coronary blood flow additional to those associated with cardiac work or oxygen consumption. Such influences were identifiable to an extent which was probably limited as much by experimental design as by the underlying physiology. Multiple regression relationships described the integrated response of coronary blood flow to the experimental challenge more completely than any univariate approach. The exercise provided useful insights into a multifactorial problem and the need for deliberate experimental design in attempting to answer specific physiological questions.

Multiple regression analysis is one small facet in a large field which has now acquired the name of "Knowledge Engineering". This embraces the use of computational methods for data processing, problem solving and decision making, and has applications in the medical field (Shortcliffe, Buchanan and Feigenbaum, 1979). Multiple regression analysis is a form of pattern recognition technique in which a data set is examined for similarities to a multiple regression model. The more flexible the model, the easier will the recognition be.

Although the technique is a relatively modest extension from single regression analysis, it is probably under-used, considering its applicability to multifactorial clinical problems (Black and Harris, 1982; Black, Harris and Judson, 1982). This paper uses multiple regression analysis as a relatively straightforward exercise to account for changes in experimentally measured coronary blood flow in terms of changes in a number of concurrently measured variables. It is always reassuring if the results of applying an unfamiliar technique can be "calibrated against" existing experience.

Foëx and his co-workers have already published some of their observations on the relationship between changes in canine coronary blood flow and changes in haemodynamics, myocardial oxygen consumption and arterial and venous blood-gas composition (Foëx et al., 1976; Foëx and Ryder, 1979, 1981; Burt and Foëx, 1979; Foëx, Ryder and Bennett, 1980). Their experimental design kept the heart *in situ*, did not separate the coronary and systemic circulations and did not exercise independent control over cardiac work and the composition of the blood supplying the myocardium. One of their observations was of an increase in coronary blood flow with hypercapnia which was disproportionate to the accompanying increase in myocardial oxygen consumption. In this respect, their conclusions, drawn from conventional univariate analysis, were consistent with those of Vance and others (1979), and different from those of Van den Bos, Drake and Noble (1979). Their data set is an ideal basis on which to examine the capabilities and limitations of a more demanding form of analysis.

## METHODS

### *Experimental techniques*

Thirty-nine dogs were studied under halothane anaesthesia. Inspired $P_{O_2}$ and $P_{CO_2}$ were changed against a background of artificial hyperventilation of the lungs. Measurements were made of arterial, left artrial and left ventricular pressures, aortic and left circumflex coronary artery blood flows and arterial and coronary venous blood-gases and pH. Foëx and colleagues have described the details of surgery and instrumentation in the publications quoted above.

Pooling four experimental series, there were 334 experimental impositions of varying combinations of inspired oxygen and carbon dioxide (table I).

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TABLE I. *The combinations of oxygen and carbon dioxide conditions considered in the study. The figures in parentheses indicate the numbers of observations obtained in the presence of beta blockade*

| Hypercapnia (7–9% $CO_2$) | Normocapnia (3–4% $CO_2$) | Hypocapnia (0% $CO_2$) | $F\mathrm{I}_{O_2}$ (%) |
|---|---|---|---|
| | | 2 | 4 |
| | 7 (6) | 4 | 6–7 |
| 9 | 34 (8) | 10 | 8–10 |
| | 19 (9) | | 15 |
| 10 | 42 (9) | 10 | 30 |
| 40 (20) | 107 (49) | 40 (20) | 100 |
| 59 (20) | 209 (81) | 66 (20) | 334 (121) |

These gave rise to corresponding combinations of high, normal or low $P\mathrm{O}_2$ with high, normal or low $P\mathrm{CO}_2$ in the arterial blood. One hundred and twenty-one of the observations were made in the presence of beta blockade induced either by metoprolol 1 mg $\mathrm{kg}^{-1}$ or oxprenolol 0.3 mg $\mathrm{kg}^{-1}$.

When the responses to each of the imposed conditions in table I had stabilized, measurements of coronary blood flow were made, and were accompanied by measurements of systemic haemodynamics and of arterial and coronary venous blood-gas compositions.

### *Data analysis: primary and derived variables*

The aortic pressure trace gave systolic, diastolic and mean values. The left ventricular trace yielded left ventricular end diastolic pressure (LVEDP) and left ventricular $\mathrm{d}P/\mathrm{d}t$. The aortic flow trace yielded stroke volume (SV) and aortic blood acceleration ($\mathrm{d}\dot{Q}/\mathrm{d}t$). Simple products of pressure and flow terms gave conventional measures of cardiac work and power (stroke volume × mean arterial pressure = left ventricular stroke work (LVSW); peak flow × systolic arterial pressure = peak left ventricular power (PLVP)).

Coronary arterial and venous $P\mathrm{O}_2$ and pH and the equations of Rossing and Cain (1966) were used to derive arterial and venous oxygen content (ml $\mathrm{dl}^{-1}$), and the product of arteriovenous oxygen content difference and the measured coronary blood flow gave the oxygen consumption of that part of the myocardium supplied by the left circumflex coronary artery.

Acid–base exchange between blood and myocardium was crudely derived in an attempt to allow any effects of changing lactate metabolism to manifest themselves. The net rate of "base uptake" or "acid output" by the myocardium was calculated as the product of coronary blood flow with that part of the arteriovenous difference in standard bicarbonate which was *not* caused by the Haldane effect. The standard bicarbonates were estimated using the $P\mathrm{CO}_2$ and pH values, and (by default of any better), the "normal" buffer line for *human* blood (Siggaard-Andersen, 1966). The contribution of the Haldane effect was estimated, in mequiv/litre of base (Siggaard-Andersen, 1966), as:

$$0.27 \times \mathrm{Hb}(S\mathrm{aO}_2 - S\mathrm{vO}_2)$$

Beta blockade was indicated by a dummy variable (BK) with a value of unity in the presence, and zero in the absence, of beta blockade (Armitage, 1971). No distinction was made between the effects of metoprolol and oxprenolol. The set of observations from each dog was accompanied by the heart weight and body weight of the dog.

A set of 19 primary and derived variables was taken from these measurements. These are listed with their symbols and reference numbers in table II.

### *The regression process: definition of terms*

Multiple regressions were carried out using the SPSS package (Nie et al., 1975), available on the Oxford University ICL 1906A computer.

The total corrected sum of squares of the flow observations is the sum of squares of the differences between the individual flow observations and the mean of the 334 observations. This will be abbreviated to TCSS for the purpose of this paper. A regression of flow observations, ($F_{\mathrm{O}}$), with a single independent variable, ($X$) determines a relationship,

$$F_r = C + M.X,$$

such that the sum of squares of the quantities ($F_o - F_r$) is reduced to a minimal "residual sum of squares". The difference between this and the TCSS is the sum of squares of the regression. The correlation coefficient ($r$) is the square root of the ratio of regression sum of squares to the TCSS.

The multiple regression of observed flow ($F_o$) determines a relationship between flow and more than one other variable, ($X_1, X_2, X_3, \ldots X_n$).

$$F_r = C + M_1.X_1 + M_2.X_2 + M_3.X_3 \ldots M_n.X_n$$

A combination of values of $C, M_1, M_2, M_3, \ldots M_n$ is found such that the sum of the quantities $(F_o - F_r)^2$ (residual sum of squares) is again minimized. The

TABLE II. *The 77 variables generated from the measured variables*

| | | Initial variable set for multiple regressions | | | |
|---|---|---|---|---|---|
| | | Variables present | | | |
| Variable name | Symbol | Variable | Reciprocal | Square | Product terms |
| Body weight | BW | 1 | | | 47 $\mathrm{BW.M\dot{v}O_2}$ |
| Heart weight | HW | 2 | | | 48 $\mathrm{HW.M\dot{v}O_2}$ |
| Arterial blood-gases | $Pa\mathrm{O_2}$ | 3 | 20 | 34 | 49 $Pa\mathrm{O_2}.Pa\mathrm{CO_2}$ |
| | $Pa\mathrm{CO_2}$ | 4 | 21 | 35 | 50 $Pa\mathrm{O_2}.\mathrm{M\dot{v}O_2}$ |
| | pHa | 5 | | | 51 $Pa\mathrm{CO_2}.\mathrm{M\dot{v}O_2}$ |
| | | | | | 52 $Pa\mathrm{O_2}.\mathrm{BK}$ |
| Venous blood-gases | $Pv\mathrm{O_2}$ | 6 | 22 | 36 | 53 $Pa\mathrm{CO_2}.\mathrm{BK}$ |
| | $Pv\mathrm{CO_2}$ | 7 | 23 | 37 | 54 $Pv\mathrm{O_2}.Pv\mathrm{CO_2}$ |
| | pHv | 8 | 24 | | 55 $Pv\mathrm{O_2}.\mathrm{pHv}$ |
| | | | | | 56 $Pv\mathrm{O_2}.\mathrm{M\dot{v}O_2}$ |
| Oxygen consumption | $\mathrm{M\dot{v}O_2}$ | 9 | 25 | 38 | 57 $Pv\mathrm{CO_2}.\mathrm{M\dot{v}O_2}$ |
| | | | | | 58 $Pv\mathrm{O_2}.\mathrm{Ac\text{-}Bas}$ |
| Acid–base exchange | Ac-Bas | 10 | 26 | 39 | 59 $Pv\mathrm{CO_2}.\mathrm{Ac\text{-}Bas}$ |
| | | | | | 60 $\mathrm{M\dot{v}O_2.BK}$ |
| Beta blockade | BK | 11 | | | 61 Ac-Bas.BK |
| | | | | | 62 $\mathrm{BK}.Pv\mathrm{O_2}$ |
| Heart rate | HR | 12 | 27 | 40 | 63 $\mathrm{BK}.Pv\mathrm{CO_2}$ |
| | | | | | 64 $\mathrm{BK}.Pv\mathrm{O_2}.Pv\mathrm{CO_2}$ |
| | | | | | 65 BK.pHv |
| LV end-diastolic pressure | LVEDP | 13 | 28 | 41 | 66 HR.MAP |
| LV d*P*/d*t* | d*P*/d*t* | 14 | 29 | 42 | 67 HR.d*Q*/d*t* |
| | | | | | 68 HR.LVEDP |
| | | | | | 69 HR.d*P*/d*t* |
| Cardiac output | $\dot{Q}$ | 15 | | | 70 d*P*/d*t*.LVSW |
| | | | | | 71 d*P*/d*t*.d*Q*/d*t* |
| Aortic acceleration | $\mathrm{d}\dot{Q}/\mathrm{d}t$ | 16 | 30 | 43 | 72 LVEDP.d*Q*/d*t* |
| | | | | | 73 PLVP.d*P*/d*t* |
| LV stroke work | LVSW | 17 | 31 | 44 | 74 LVEDP.MAP |
| Peak LV Power | PLVP | 18 | 32 | 45 | 75 d*P*/d*t*.MAP |
| | | | | | 76 MAP.d*Q*/d*t* |
| Mean arterial pressure | MAP | 19 | 33 | 46 | 77 LVEDP.d*P*/d*t* |

difference between the residual and total corrected sum of squares is the *multiple* regression sum of squares, and the ratio of the latter to the TCSS is the square of the *multiple* correlation coefficient, multiple $r^2$. The multiple $r^2$ is one measure of completeness of the description provided by the multiple regression equation, although other measures may give different impressions of completeness (see Results).

The coefficients $M_1$, $M_2$, $M_3$, . . . $M_n$ are the regression coefficients. The terms $X_1, X_2, X_3, \ldots X_n$, contribute significantly to the multiple regression to the extent that their regression coefficients are significantly different from zero. This will not occur if a variable $X_i$ is totally unrelated to flow, nor if its descriptive effect is completely contained in the descriptive effect of another variable to which $X_i$ is closely related. Merely offering a large number of variables to the regression process does not mean that every variable will be incorporated with significant effect into the multiple regression relationship. It does not create relationships which do not exist. Unimportant terms are effectively ignored by allocating them regression coefficients which are not significantly different from zero.

It may be, however, that, if variables $X_p$ and $X_q$ are very closely related to each other, the regression process may include $X_p$ in the regression and "ignore" $X_q$, even though the latter is more directly related in a *causal* sense to changes in flow. A reason for incorporating the term $X_p$ instead of $X_q$ would be if it had been measured with greater precision. Nonetheless, the *descriptive* relationship between $X_p$ and flow would be a valid one.

*The expansion of the variable set*

The ability of the regression process to recognize similarities of pattern between a data set and a regression model depends somewhat on the flexibility of the regression model. If, for instance, the relationship between coronary blood flow and coronary venous $PO_2$ were markedly non-linear and the regression model allowed only for a *linear* relationship, pattern recognition would be less successful than if the model *did* allow for non-linearities. The inclusion of square and reciprocal terms in coronary venous $PO_2$ ($Pv_{O_2}$) would make this allowance sufficiently well for many practical purposes. Thus the data could be examined for similarity to an equation of the form:

$$F_r = C + M_1.Pv_{O_2} + M_2.(1/Pv_{O_2}) + M_3.(Pv_{O_2})^2.$$

If the relationship was predominantly linear, the inclusion of the non-linear terms would not improve the description, but in the presence of non-linearities, it would.

By extension of this reasoning, square and reciprocal terms were added to most of the primary and derived variables in table II. The reciprocal and square terms are included in the same table.

The product terms listed in table II are an attempt to confer additional flexibility on the regression model by relaxing the restriction that the effect of every variable should be independent of the values assumed by other variables. If, for instance, the regression process was constrained to examine the data set for similarity to a relationship between flow, $Pv_{O_2}$ and $Pv_{CO_2}$ which had the form:

$$F_r = C + M_1.Pv_{O_2} + M_2.Pv_{CO_2}$$

then the effect of a change of $Pv_{CO_2}$ ($\Delta Pv_{CO_2}$) would be $M_2.\Delta Pv_{CO_2}$, irrespective of the prevailing $Pv_{O_2}$. Provision for a term $M_3.(Pv_{O_2} \times Pv_{CO_2})$ to be included in the above equation would allow the regression process to search for a similarity (if it existed) to a regression model in which the effect of a change in $Pv_{CO_2}$ *could* vary with $Pv_{O_2}$.

A similar logic applies to the inclusion of the product terms with the dummy variable BK. A regression model which allows for a relationship:

$$F_r = C + M_1.Pv_{O_2} + M_2(\text{BK} \times Pv_{O_2}) + M_3.\text{BK}$$

allows both the slope and the intercept of the flow to $Pv_{O_2}$ relationship to be varied by beta-blockade.

Anomalies in the inclusion of reciprocal, square and product terms in table II reflect the empirical development of the study as new possibilities for flexibility were successively realized. The addition of new variables ceased when it became clear that many variables could be omitted from the 77-variable regression without noticeable detriment to the explanation of the TCSS of the flow observations. The description of the changes in flow was as complete as could be achieved in terms of the associated variables which had been measured.

*Analysis of TCSS by "backwards regression"*

If, in order to allow for non-linear and interactive descriptive effects, a given "primary" variable is represented additionally by its reciprocal, square and product terms, its overall contribution cannot readily be examined by the contributions of its individual terms. What is required is to compare the regression sum of squares (or multiple $r^2$) for a regression which includes *all* the terms in that "primary" variable with that for a regression which is similar except that it contains *none* of the terms. If the term "backwards regression" (Nie et al., 1975) is applied to the procedure in which regression sums of squares are compared for relationships with and without *individual* terms, "backwards regression by groups" might be used to describe the modification proposed above.

"Backwards regression by groups" lies behind much of this study. The "groups" or categories used were: Myocardial oxygen consumption (Mv), haemodynamics (Haem), arterial blood-gases (Pa), coronary venous blood-gases (Pv), arterial and venous pH terms (pH), acid–base transfer (Ac-Bas), beta-blockade (BK), heart weight (HW) and body weight (BW). The variables in each group or category are indicated in table III by reference to the numbers listed in table II.

The SPSS multiple regression package was used to determine a selection of regression sums of squares whose interrelationships allow an analysis of the observed TCSS of coronary blood flow.

## RESULTS AND DISCUSSION

*Control of coronary blood flow*

The particular selection of results has been determined by consideration of the background physiology of the control of coronary blood flow. The considerable complexities of coronary vascular control at cellular level are beyond the scope of this study, and are well reviewed elsewhere (Berne, 1964; Rubio

TABLE III. *The contents of the variable categories by reference to the variables listed and numbered in table II*

| Category name | Symbols | Variable numbers contained | Total |
|---|---|---|---|
| Myocardial $O_2$ consumption | Mv | 9, 25, 38, 47, 48, 50, 51, 56, 57, 60 | 10 |
| Haemodynamics | Haem | 12–19, 27–33, 40–46, 66–77 | 34 |
| Arterial blood-gases | Pa | 3, 4, 20, 21, 34, 35, 49–53 | 11 |
| Coronary venous blood-gases | Pv | 6, 7, 22, 23, 36, 37, 54–59, 62–64 | 15 |
| Arterial $P_{O_2}$ | $Pa_{O_2}$ | 3, 20, 34, 49, 50, 52 | 6 |
| Arterial $P_{CO_2}$ | $Pa_{CO_2}$ | 4, 21, 35, 49, 51, 53 | 6 |
| Coronary venous $P_{O_2}$ | $Pv_{O_2}$ | 6, 22, 36, 54, 55, 56, 58, 62, 64 | 9 |
| Coronary venous $P_{CO_2}$ | $Pv_{CO_2}$ | 7, 23, 37, 54, 57, 59, 63, 64 | 8 |
| pH | pH | 5, 8, 24, 55, 65 | 5 |
| Acid–base exchange | Ac-Bas | 10, 26, 39, 58, 59, 61 | 6 |
| Beta blockade | BK | 11, 52, 53, 60–65 | 9 |
| Heart weight | HW | 1, 47 | 2 |
| Body weight | BW | 2, 48 | 2 |

and Berne, 1975; Belloni, 1979). This data set can only address the problem at a more simplistic level. The close and long recognized association between changes in coronary blood flow and changes in myocardial oxygen consumption (Eckenhoff et al., 1947), raises the question of whether the latter, or the cardiac work rate which it represents, is also a direct *cause* of the former. A finding that coronary blood flow is *uniquely* dependent on myocardial oxygen consumption would suggest that this may be so — that is that some process very closely related to cellular energy utilization or oxidative energy production is on the final common pathway in the mechanisms of coronary vascular control.

If the relationship between coronary blood flow and myocardial oxygen consumption is not unique, but can be modified by factors unrelated to cardiac work, alternative hypotheses can be entertained. At constant rates of oxygen supply (coronary blood flow times arterial oxygen content) changes in myocardial oxygen consumption will alter the amount of oxygen in the coronary venous blood, and the $P_{O_2}$ in the myocardial tissue. The associated changes in carbon dioxide production would also change myocardial tissue $P_{CO_2}$ and pH. Therefore myocardial chemosensitivity to $P_{O_2}$, $P_{CO_2}$ and pH could conceivably be partly or wholly responsible for the observed changes in coronary blood flow with changes in myocardial oxygen consumption.

With observations from this data set, it can be shown that the relationship between coronary blood flow and oxygen consumption is not unique. On two-dimensional plots of coronary blood flow against oxygen consumption, combinations of coronary venous hypoxia and hypercapnia can be found in which the blood flow/oxygen consumption relationship is displaced. However, such plots cannot distinguish if the displacement is attributable uniquely to the changes in the coronary venous blood, if changes in the arterial blood are more closely related, or if, even, they can be a result of changes in cardiac work which fail, in some unforeseen way, to be represented by the oxygen consumption. The multiple regression approach was adopted in the hope of achieving a different insight on the problem.

### *The most complete regression description*

The coronary blood flow observations covered a wide range. The mean was 28.34 ml min$^{-1}$ (SD 20.56) and the TCSS of flow was 140 737. The regression of coronary blood flow on all 77 variables in table III had a regression sum of squares of 136 740, and thus accounted for 97.16% of the TCSS of flow. This appears satisfactorily complete, as judged by a multiple $r^2$ of 0.9716, and even more complete as judged by a multiple correlation coefficient (multiple $r$) of 0.9857 (the square root of 0.9716). However, these figures correspond to a residual standard deviation of 4 ml min$^{-1}$. Thus only 80.8% of the *standard deviation* of the flow observations is accounted for. The analysis is carried out in terms of sums of squares, since these have additive properties, but residual standard deviations are also displayed in table IV to provide an alternative impression of the completeness of the explanations of the variability of flow.

Although the distribution of the flow observations is clearly not normal, their distribution about the regressions appears to be tolerably so, although

TABLE IV. *The effect of omitting single variable categories in turn from the 72-variable regression containing all but the pH variables.* • *in the column under the name of the variable category indicates that that category is represented amongst the regression variables. The category named in each row has been omitted from the regression. By reference to the letters (A, B, C, etc) above the columns on the right of the table, the* F *statistic, (E), is calculated as C/(DG), where G is (140737 − B)/(333 − A). Residual standard deviation is $\sqrt{G}$. The* P *value, (F), is that associated with the* F *statistic for D and (333 − A) degrees of freedom)*

| | | | | | | | | | | *A* | *B* | *C* | *D* | *E* | *F* | *G* | *H* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $O_2$ consump. | $Pa_{CO_2}$ | $Pv_{CO_2}$ | $Pa_{O_2}$ | $Pv_{O_2}$ | Haemo- dynam. | Acid-base exchange | β-blockade | Heart wt | Body wt | No. vari-ables | Regression SS | Change regression SS | No. variables removed | *F* | *P* | Residual mean square | Residual SD |
| • | • | • | • | • | • | • | • | • | • | 72 | 136 280 | — | — | | | 17 | 4.1 |
| • | • | • | • | • | • | • | • | • | BW | 70 | 136 263 | 17 | 2 | 0.5 | >0.25 | 17 | 4.1 |
| • | • | • | • | • | • | • | • | HW | • | 70 | 136 232 | 48 | 2 | 1.4 | >0.10 | 17 | 4.1 |
| • | • | • | • | • | • | • | BK | • | • | 64 | 135 967 | 313 | 8 | 2.17 | <0.05 | 18 | 4.2 |
| • | • | • | • | • | • | AB | • | • | • | 66 | 135 531 | 749 | 6 | 6.57 | <0.001 | 19 | 4.4 |
| • | • | • | • | • | HM | • | • | • | • | 38 | 135 027 | 1253 | 34 | 1.79 | <0.01 | 19 | 4.4 |
| • | • | • | • | PVO | • | • | • | • | • | 64 | 134 394 | 1886 | 8 | 9.82 | 0.001 | 24 | 4.9 |
| • | • | • | Pao | • | • | • | • | • | • | 66 | 133 863 | 2417 | 6 | 15.49 | 0.001 | 26 | 5.1 |
| • | • | PvC | • | • | • | • | • | • | • | 64 | 133 073 | 3207 | 8 | 14.31 | 0.001 | 28 | 5.3 |
| • | PaC | • | • | • | • | • | • | • | • | 66 | 130 815 | 5465 | 6 | 24.6 | 0.001 | 37 | 6.1 |
| Mv | • | • | • | • | • | • | • | • | • | 62 | 120 375 | 15905 | 10 | 21.2 | <0.001 | 75 | 8.7 |

this has not been rigourously tested.

*Elimination of redundant variables*

Although the regression of all 77 variables in table III on coronary blood flow satisfactorily explains most of the TCSS of flow, it is extremely cumbersome. The next step was to reduce it by paring away redundant variables.

The first backwards regression was performed to eliminate the category of pH variables. As no deliberate attempt was made to change pH independently of $P\text{CO}_2$, the explanatory effect of the pH category was expected to be largely contained in that of the $P\text{CO}_2$ terms. Removal of the five pH variables changed the regression sum of squares by only 0.33% of the TCSS of flow. The explanation provided by the resulting 72-variable regression was still satisfactorily complete (multiple $r^2 = 0.9683$).

Table IV compares the sum of squares for this 72-variable regression with the sums of squares for the regressions in which the other variable categories have been omitted, one at a time. The top line of solid circles indicates that every one of the overlying variables was represented (72 variables in all). The next line has solid circles under every category except BW, indicating that the two body weight variables have been removed, leaving a regression of 70 variables. In the next line, only the two heart weight variables have been removed; in the next, only the eight beta blockade variables, and so on. The changes in regression sums of squares from that of the 72-variable regression are a measure of the portion of the explanation of TCSS which is provided *uniquely* by each variable category, without overlap from any other category in table IV. The sum of the unique contributions from all variable categories accounts for only 22% of the TCSS of flow. Thus three-quarters of the explanation of TCSS is provided by overlapping contributions from more than one variable category. None of the categories BW, HW, BK, Haem or Ac-Bas makes a unique contribution greater than 0.6% of the TCSS of flow, and the sum of their unique contributions explains only 1.75%. For each variable category, table IV also shows the probability, *P*, that its unique contribution is *not* a significant improvement to the explanation of the TCSS. By these measures, even the small contributions of BK, Ac-Bas and Haem appeared to be *statistically* significant ($P < 0.05$), (as indeed was the contribution of the pH category to the 77-variable regression). Statistical significance indicates consistency of observation rather than physiological importance. For the purposes of later discussion, the categories HW, BW, pH, BK and Ac-Bas were declared redundant, although some interest was retained in the haemodynamic variables.

The pH variables were "redundant" in regressions containing $P\text{CO}_2$ variables, but their contribution was seven-fold larger in regressions which did not. As expected, the explanatory effect of pH variables was largely overlapped by that of the $P\text{CO}_2$ variables. In similar fashion, the explanatory effects of the beta blockade variables and the HW and BW variables were shown to be largely covered by those of the oxygen consumption variables.

After excluding the categories pH, HW, BW, Ac-Bas and Haem, 21 variables were left in the categories Mv, Pa and Pv. These are the variables listed for Mv, Pa, and Pv in table III, without the product terms with variables in the other categories. These 21 variables accounted for 94.5% of the explanation of TCSS, or 75% of the standard deviation of flow.

*"Extended backwards regression"—Venn diagrams*

The "backwards regression by groups" in table IV was adequate to delineate the unique explanatory contributions of the different variable categories. It was "extended" to describe also the areas of *overlap* between the explanatory contributions.

Table V illustrates an "extended backwards regression" applied to the explanatory contributions from the three variable categories—Mv, Pa and Pv. The analysis is detailed in the appendix. It requires the sums of squares of seven regressions (the regression containing all three variable categories, the three regressions containing two out of the three, and the three containing only one category each). From these, it calculates seven portions of the explanation (three portions of unique contribution, three portions of overlap between explanationatory contributions from two of the three categories and one portion of overlap between all three categories). The interrelationships of these areas are displayed in figure 1 using a Venn diagram.

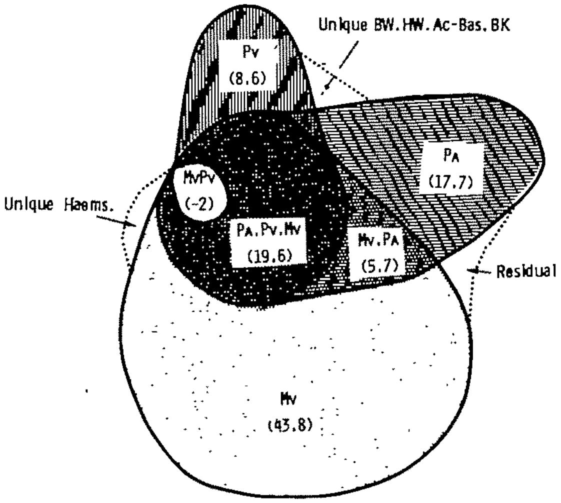

FIG. 1. Explanatory contributions to TCSS of coronary blood flow (Pa, Pv and Mv variables) including inter-animal variation: the Venn diagram corresponding to table V, with unique contributions of additional variable categories contained by dotted lines. The labels in each area denote the category or categories explaining that area of TCSS, with the corresponding percentage of TCSS explained.

TABLE V. *The relationships of the descriptive contributions of Mv, Pa and Pv categories. Seven regression sums of squares (first column) are required to define the percentage of the TCSS of flow explained by the overlap between all three categories (last column, row 1) by the three two category overlaps (last column, rows 2, 3 and 4) and the three unique contributions (last column, rows 5, 6 and 7). The required calculations are given in the Appendix*

| Regression sum of squares | Multiple $r^2$ | Variable categories | | | Percentage of flow TCSS explained |
|---|---|---|---|---|---|
| | | Mv | Pa | Pv | |
| 132 996 | 94.5 | • | • | • | 19.6 |
| 120 974 | 86.0 | • | • | — | 5.7 |
| 108 121 | 76.8 | • | — | • | −2.0 |
| 71 366 | 50.7 | — | • | • | 1.0 |
| 38 405 | 27.3 | — | — | • | 8.7 |
| 62 013 | 44.1 | — | • | — | 17.7 |
| 94 488 | 67.1 | • | — | — | 43.8 |
| Total | | | | | 94.5 |

An even more extended backwards regression, requiring 15 regressions and defining 15 portions of explanation, allows the explanatory effects of the haemodynamic variables to be located in relation to those of the Mv, Pa and Pv categories. In figure 2, the explanatory effects of the latter three categories are portrayed similarly to their portrayal in figure 1. The superimposed explanatory effect of the haemodynamic terms encroaches on, and so reduces the unique explanatory contributions of the Mv, Pa and Pv terms in comparison with figure 1.

It would have been interesting to separate the effects of $Pa_{O_2}$ from those of $Pa_{CO_2}$, and $Pv_{O_2}$ from $Pv_{CO_2}$, in a six-category Venn diagram. However, this would require the sums of squares of 63 regressions to delineate 63 portions of the explanation in order to draw a Venn diagram which would be indecipherable. In any case figures 1 and 2 are sufficient for the present discussion.

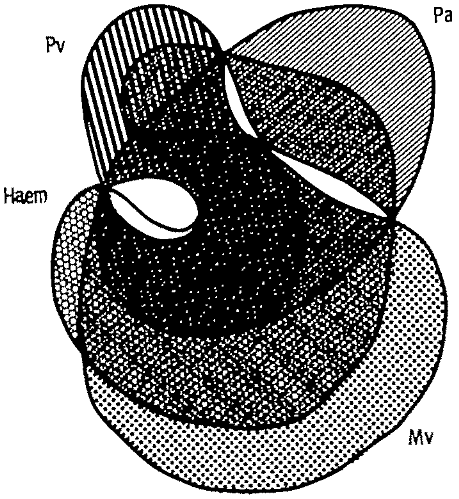

FIG. 2. Explanatory contributions to TCSS of coronary blood flow (Pa, Pv, Mv and Haem) including inter-animal variations: the Venn diagram for the categories Mv, Pa, Pv and Haem. There is insufficient room for comprehensive labelling, but the labels can be inferred from figure 1.

*Inferences from the Venn diagrams*

If the explanatory effects of total cardiac work on changes in coronary blood flow are encompassed within those of oxygen consumption, any explanatory effects outside those of oxygen consumption might be regarded as being unrelated to cardiac work. On this basis, one would argue from figure 1 that 26% of the TCSS of flow is unrelated to cardiac work. Twenty-six percent is the sum of the unique contributions of Pa terms, the Pv terms and the Pa/Pv overlap (see table V). However, figure 2 shows that a portion of the explanatory effects of the *haemodynamic* terms are also outside those of the oxygen consumption terms. Their encroachment on the effects of the Pa and Pv categories is such as to reduce the sum of the Pa, Pv and Pa/Pv effects to only 14% of the TCSS of flow. The extensive areas of overlap between the explanatory contributions of terms related (Mv and Haem) and unrelated (Pa and Pv) to cardiac work are unhelpful in this context, since they cannot distinguish which terms might be more closely related to the flow changes.

The extension of the explanatory contribution of the haemodynamic terms beyond those of oxygen consumption requires further thought. Although it is perfectly possible to calculate the rate at which the heart performs *external* work on the blood which it pumps, that external work is a poor predictor of oxygen consumption of intact hearts *in situ* (Braunwald, 1969; Gibbs, 1978). The oxygen consumption is affected also by the *internal* work required to maintain, amongst other things, given ventricular pressures at different degrees of dilatation. Happily, the approach in this study is unaffected by these difficulties. A conglomerate of haemodynamic variables was offered to the regression so as to determine an empirical relationship which accounted for as much as possible of the TCSS of flow. A more informed choice of variables might have been more effective, but subsidiary investigation has not proved this. In any case, the problem is that the explanatory effects of the haemodynamic terms seem already *too* extensive.

If cardiac work and the associated oxygen consumption affect myocardial conductance, the additional explanatory effects of the haemodynamic terms may be attributable to their representation of myocardial perfusion pressure. As myocardial vascular conductance and perfusion pressure both vary during the cardiac cycle, this explanation cannot be satisfactorily tested. All that can be argued is that the inclusion of the haemodynamic terms reduces the percentage of the TCSS of flow which cannot be explained in terms of cardiac work, oxygen consumption *or* myocardial perfusion pressure.

The unique explanatory contributions of $Pv_{O_2}$, $Pv_{CO_2}$, $Pa_{O_2}$ and $Pa_{CO_2}$ are very highly significant, but relatively small. Their smallness allows conflicting arguments as to the importance of factors unrelated to cardiac work in the control of coronary blood flow.

One may dismiss the explanatory effects, arguing that the deficiencies in the account given by oxygen consumption for changes in coronary blood flow are the result of systematic errors in estimation of arteriovenous difference in oxygen content; these errors are, in turn, systematically linked to the Pa and Pv variables by consistent inaccuracies in blood-gas analysis or the equation of Rossing and Cain (1966).

Alternatively, one might argue that the changes in Pa and Pv terms *do* have effects in their own right, but that these have been largely obscured by the experimental design in this study; the concurrence of changes related and unrelated to cardiac work has been too extensive to enable their effects to be adequately separated. In a different experimental design, Case and Greenberg (1976) and Case and colleagues (1978), perfused the coronary vasculature separately from the systemic circulation so that myocardial $P_{O_2}$ and $P_{CO_2}$ could be changed without change in cardiac work or oxygen consumption. Changes in coronary vascular conductance were observed which could now be related only to blood-gas changes.

### *Subsidiary considerations*

*"Negative overlap".* Table V shows that the Mv/Pv overlap has negative sign. For want of better means, such "negative overlaps" are depicted as "holes" in the Venn diagrams (figs 1, 2).

The explanation of this needs a simpler example. For the single categories, $Pa_{O_2}$ and $Pv_{O_2}$, the respective regression sums of squares are 43062 and 23410. If there were no overlap between the explanatory effects of $Pa_{O_2}$ and $Pv_{O_2}$, one would expect the two category regression with $Pa_{O_2}$ and $Pv_{O_2}$ to have a sum of squares of 43062 plus 24410, which equals 67472. Since the regression actually has a smaller sum of squares (55090), the expected-minus-observed difference of 12382 has *positive* sign and is attributed to *positive* overlap between the explanatory effects of $Pa_{O_2}$ and $Pv_{O_2}$.

The regression with the $Pa_{CO_2}$ variables has a sum of squares of 11545. The two category regression with $Pa_{O_2}$ and $Pa_{CO_2}$ terms has an observed sum of squares of 62013. This is considerably more than the expected value of 54607 (43062 plus 11545) for the absence of overlap. The negative sign of the expected-minus-observed difference is *negative* overlap, arising because of supra-additive explanatory interaction between the variable categories $Pa_{O_2}$ and $Pa_{CO_2}$.

More complex overlaps are hard to explain and depict, but they do not affect the main inferences based (above) on the unique explanatory contributions of the Pa and Pv terms.

*Inevitable correlation.* Myocardial oxygen consumption was calculated as the product of a varying coronary blood flow and an arteriovenous oxygen content difference. If the latter had been constant the correlation of oxygen consumption with flow would have been perfect. Variation in arteriovenous oxygen content difference rendered the correlation less than perfect, although still strong. Some of the strength will have arisen from the inevitable correlation of flow, as dependent variable, with the flow term contained in the oxygen consumption. Any variations in flow will affect both sides of the regression equation and such variations will include inter-animal variation, random variation and measurement error.

Inter-animal variation can be allowed for by a variety of approaches based on the examination, for each animal, of the discrepancies between the observations and the expectations from the regression relationships. When such allowance is made, the TCSS of the flow observations is reduced, but the percentages explained by corresponding regressions remain largely similar, except as expected, for a particular reduction of the explanatory contribution which is unique to myocardial oxygen consumption.

Even after allowance for inter-animal variation, random and error variation in flow will still artificially strengthen the relationship between flow and oxygen consumption, but they are not necessarily major factors. It will be noted the AB terms also consisted of the product of coronary blood flow with an arteriovenous difference. Although inevitable correlation may be held responsible for the significance of the unique explanatory contribution of the AB terms, this contribution constituted a very small proportion of the TCSS.

## CONCLUSIONS

The application of multiple regression analysis to the data available for this study has satisfied one requirement of an exercise with an unfamiliar technique — in *not* contradicting the conclusions reached in previous publications. The conclusions are broadly consistent with concepts derived from more disruptive experimentation. Multiple regressions have afforded an extraordinarily complete account of the observed variation in flow, compared with univariate approaches, and have yielded penetrating insights into the overlapping accounts rendered by interdependent explanatory variables. The relatively small proportion of the flow variation which seems not to be related to cardiac work reaffirms that no approach to data analysis can obviate the need for experimental design aimed directly at the problems to be solved. The design in this study was aimed at more general aspects of cardiovascular control.

There are many clinical problems which do not allow the option of corroboration by more invasive and disruptive approaches. For such problems, a more penetrating approach to data analysis may be the only way to do justice to the data set.

## APPENDIX

### UNIQUE AND OVERLAPPING EXPLANATORY CONTRIBUTIONS OF CATEGORIES MV, PA AND PV (TABLE V)

The explanation provided by the Pa, Pv and Mv categories in combination is the sum of squares of the regression containing the terms in all three categories (that is 132 996, or 94.5% of the TCSS of flow).

The unique contribution of a given variable category is the difference between 132 996 and the sum of squares for the two-category regression which excludes that variable. The regression using Pa and Mv terms excludes Pv terms and has a sum of squares of 120 794. Thus the unique contribution of the Pv category is

132 996 − 120 794 = 12 202 (or 8.7% of the TCSS)

Similarly, the unique contributions of Pa and Mv are, respectively, 24 875 and 61 630 (or 17.7% and 43.8% of the TCSS).

The entire explanatory contribution made by a single variable category is the sum of squares for the regression containing only that category. For the Pv, Pa and Mv categories these are, respectively, 38 405, 62 013 and 94 488 (or 27.3%, 44.1% and 67.1% of the TCSS).

Thus (38 405 − 12 202 = 26 203) of the Pv contribution is not unique, but is overlapped by at least one of the other two categories.

The amount by which Mv, alone and in combination with Pa, overlaps Pv is given by the difference between the sum of the total Pv and Mv contributions (38 405 + 94 408), and the sum of squares (108 121) of the two-category regression using Pv and Mv categories together:

38 405 + 94 408 − 108 121 = 24 772

Since 24 772 of the overlapped contribution of Pv (26 023), is overlapped by Mv, the remainder,

26 023 − 24 772 = 1431 (1% of TCSS)

is the amount by which Pa alone overlaps Pv.

By similar reasoning, the amount by which Mv alone overlaps Pa is 8086 (or 5.7% of TCSS), and the amount by which Mv alone overlaps Pv is −2849, (or −2% of TCSS).

The above reasoning defines six of the seven portions of the explanation of TCSS. These are three unique contributions (Pv, Pa, and Mv) and three explanatory overlaps between two categories (Pa and Pv, Mv and Pa, and Mv and Pv). The remaining portion is the three-category explanatory overlap (Mv and Pa and Pv), which is the difference between the sum of squares for the three-category regression and the sum of the squares of the six portions of the description already defined:

132 996 − 105 375 = 27 621 (or 19.6% of TCSS).

A more extensive process, using similar reasoning, defines the 15 portions of explanation obtainable from a four-category regression.

### ACKNOWLEDGEMENTS

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### REFERENCES

Armitage, P. (1971). *Statistical Methods in Medical Research*, 4th edn. Oxford: Blackwell Scientific Publications.

Belloni, F. L. (1979). The local control of coronary blood flow. *Cardiovasc. Res.*, **13**, 63.

Berne, R. M. (1964). Regulation of coronary blood flow. *Physiol. Rev.*, **44**, 1.

Black, A. M. S., and Harris, R. I. (1982). Comparing two head injury treatments by linear logistic model. *Acta Neurochir.*, **62**, 31.

Black, A. M. S., Harris, R. I., and Judson, J. A. (1982). A model based description of a head injury treatment. *Acta Neurochir.*, **60**, 265.

Braunwald, E. (1969). The determinants of myocardial oxygen consumption. *Physiologist*, **12**, 65.

Burt, G., and Foëx, P. (1979). The effects of metoprolol on systemic haemodynamics, myocardial performance and the coronary circulation during halothane anaesthesia. *Br. J. Anaesth.*, **51**, 829.

Case, R. B., Felix, A., Wachter, M., Kyriakidis, G., and Castellana, F. (1978). Relative effect of $CO_2$ on canine coronary vascular resistance. *Circ. Res.*, **42**, 410.

—— Greenberg, H. (1976). The response of canine coronary vascular resistance to local alterations in coronary arterial $P_{CO_2}$. *Circ. Res.*, **39**, 558.

Eckenhoff, J. E., Hafkenschiel, J. H., Landmesser, C. M., and Harmel, M. (1947). Cardiac oxygen metabolism and control of the coronary circulation. *Am. J. Physiol.*, **149**, 634.

Foëx, P., and Ryder, W. A. (1979). Effect of $CO_2$ on the systemic and coronary circulations and on coronary sinus blood gas tensions. *Bull. Eur. Physiopath. Resp.*, **15**, 625.

—— —— (1981). Interactions of adrenergic beta receptor blockade (oxprenolol) and $P_{CO_2}$. in the anaesthetized dog: influence of intrinsic beta-sympathetic activity. *Br. J. Anaesth.*, **53**, 19.

—— —— Bennet, M. J. (1980). Carbon dioxide and coronary blood flow: direct effects or consequences of altered dynamics of the systemic circulation. *Bull. Eur. Physiopath. Resp.*, **16**, 185.

—— Saner, C. A., Fordham, R. M. M., Roberts, J. G., and Bennet, M. J. (1976). Le lavage du $CO_2$ myocardique: un facteur d'augmentation de la performance cardiaque en cas d'hypoxie. *Bull. Eur. Physiopath. Resp.*, **12**, 231.

Gibbs, C. I., (1978). Cardiac energetics. *Physiol. Rev.*, **58**, 174.

Nie, N. H., Hadlaihull, C., Jenkins, J. G., Steinbrenner, K, and Bent, D. H. (1975). *Statistical Packages for the Social Sciences*, 2nd edn. New York: McGraw-Hill.

Rossing, R. G., and Cain, S. M. (1966). A nomogram relating $P_{O_2}$, pH, temperature and hemoglobin saturation in the dog. *J. Appl. Physiol.*, 21, 195.
Rubio, R., and Berne, R. (1975). Regulation of coronary blood flow. *Prog. Cardiovasc. Dis.*, 18, 105.
Siggaard-Andersen, O. (1966). *The Acid-Base Status of the Blood*, 3rd edn. Copenhagen: Munksgaard.
Shortcliffe, E. H., Buchanan, B. G., and Feigenbaum, E. A. (1979). Knowledge engineering for medical decision making: a review of computer based decision aids. *Proc. IEEE*, 67, 1207.
Vance, J. P., Smith, G., Brown, D. M., and Thornburn, J. (1979). Response of mean and phasic coronary arterial blood flow to graded hypercapnia in dogs. *Br. J. Anaesth.*, 51, 523.
Van den Bos, G. C., Drake, A. J., and Noble, M. I. M. (1979). The effect of carbon dioxide upon myocardial contractile performance, blood flow and oxygen consumption. *J. Physiol. (Lond.)*, 287, 141.

## QUELQUES POSSIBILITES ET LIMITATIONS DE L'ANALYSE DE REGRESSION MULTIPLE: APPLICATION AU DEBIT SANGUIN CORONAIRE CHEZ LE CHIEN

### RESUME

Les modifications des concentrations d'oxygène et de gaz carbonique inspirées ont entraîné des modifications des paramètres hémodynamiques systémiques et coronaires chez 39 chiens anesthésiés. Ces modifications ont constitué la base de données pour un exercice d'analyse de régression multiple utilisant les conditionnements SPSS. Le problème physiologique était d'identifier des facteurs agissant sur le débit sanguin coronaire en plus de ceux associés au travail cardiaque ou à la consommation d'oxygène. De tels facteurs ont pû être retrouvés dans une mesure probablement limitée autant par le schéma expérimental que par la physiologie sous-jacente. Les relations de régression multiple décrivaient la réponse intégrée du débit sanguin coronaire au protocole expérimental de façon plus complète que n'importe quelle approche à une seule variable. L'exercice a fourni des données utiles sur un problème multifactoriel et a montré la nécessité de schémas expérimentaux réfléchis pour tenter de répondre à des questions spécifiques en physiologie.

## EINIGE FÄHIGKEITEN UND GRENZEN DER MULTIPLEN REGRESSIONSANALYSE. ANWENDUNG AUF DEN BLUTSTROM IN DEN KORONARIEN DES HUNDES

### ZUSAMMENFASSUNG

Veränderungen der eingeatmeten Sauerstoff- und Kohlendioxid-Konzentration gingen mit Veränderungen der systemischen und koronaren Hämodynamik bei 39 narkotisierten Hunden einher. Diese Veränderungen lieferten die Datengrundlage für eine Übung in multipler Regressionsanalyse unter Benutzung von SPSS Packungen. Das physiologische Problem war es, die Einflüße auf den koronaren Blutstrom herauszufinden, die zusätzlich zu den mit der Herztätigkeit oder dem Sauerstoffverbrauch zusammenhängenden auftraten. Solche Einflüße konnten bis zu einem Grad herausgefunden werden, der wahrscheinlich genausoviel vom experimentellen Design, wie durch die zu Grunde liegende Physiologie begrenzt war. Die multiplen Regressionsbeziehungen beschrieben die integrierte Reaktion des koronaren Blutstromes auf den experimentellen Reiz umfassender, als jedes Vorgehen mit nur einer Variablen. Die Übung verschaffte nützliche Einsichten in ein multifaktorielles Problem und die Notwendigkeit einer bestimmten experimentellen Anordnung, wenn man eine Antwort auf spezielle physiologische Fragen erhalten will.

## ALGUNAS POSIBILIDADES Y LIMITACIONES DEL ANÁLISIS DE REGRESION MUTIPLE: APLICACIÓN A LA CORRIENTE SANGUÍNEA CORONARIA DE LOS CANES

### SUMARIO

En 39 perros anestesiados, los cambios de concentración de anhídrido carbónico y oxígeno inspirado tuvieron por efecto modificaciones de la hemodinámica sistémica y coronaria. Estos cambios suministraron la base de datos de un ejercicio en el marco de un análisis de regresión múltiple en el que se usó los conjuntos SPSS. El problema fisiológico consistía en identificar las influencias sobre la corriente sanguínea coronaria que se sobreponen a las asociadas con el consumo de oxígeno o la actividad cárdiaca. Dichas influencias pudieron ser identificadas en una medida probablemente limitada tanto por el diseño experimental cómo por la fisiología subyacente. Las relaciones de regresión múltiple describieron la respuesta integrada de la corriente sanguínea coronaria al estímulo experimental de manera más cabal que la de cualquier enfoque univariable. El ejercicio suministró unos conocimientos íntimos útiles de un problema multifactorial y la necesidad de un diseño experimental deliberado con miras a dar una respuesta a unos interrogantes fisiológicos específicos.

*Br. J. Anaesth.* (1982), 54, 1331

# SUXAMETHONIUM ASSOCIATED HYPERTONICITY AND CARDIAC ARREST IN UNSUSPECTED PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY

S. P. K. LINTER, P. R. THOMAS, P. S. WITHINGTON AND M. G. HALL

## SUMMARY

We report a case that showed many of the features of the malignant hyperpyrexia syndrome following suxamethonium administration, in an unsuspected case of pseudohypertrophic (Duchenne) muscular dystrophy.

In 1971 a patient with suxamethonium-induced cardiac arrest in an unsuspected case of pseudohypertrophic muscular dystrophy was described (Genever, 1971). Suxamethonium has been implicated in several cases of muscular rigidity, hyperkalaemia and cardiac arrest and in malignant hyperpyrexia, and there is evidence that these reactions occur often when there are pre-existing muscular disorders including muscular dystrophies, hernias (Ellis and Halsall, 1980) and strabismus (Tammistoa et al., 1970). The mechanisms are unknown.

A second patient with cardiac arrest in unsuspected pseudohypertrophic (Duchenne) muscular dystrophy is reported in this paper. In this case, however, there was a significant difference in that cardiac arrest was preceded by rigidity, cyanosis and acidosis.

## CASE HISTORY

A male, only child, who had not walked until the age of 2 yr, but who had been healthy and considered normal by his parents, was admitted to hospital at the age of 5 yr for surgical correction of his right convergent squint which he had developed at the age of 2 yr. He had not been investigated for his delay in walking.

The patient was premedicated with papaveretum 5 mg and hyoscine 100 μg. After induction of anaesthesia with nitrous oxide, oxygen, cyclopropane and halothane he was given suxamethonium 25 mg i.v. and immediately developed generalized hypertonicity, such that it was difficult to open his mouth and, after intubation of the trachea, to inflate the lungs. Despite ventilation with 100% oxygen the patient became progressively more cyanosed with bradycardia, and seven minutes after the suxamethonium there was cardiac arrest. Resuscitation from asystole included treatment with i.v. sodium bicarbonate and adrenaline followed by intracardiac adrenaline and calcium gluconate before defibrillation for ventricular fibrillation resulted in sinus rhythm.

Thirty minutes after the intracardiac injection and about forty minutes after the suxamethonium the patient was rousable and the heart was in sinus rhythm with multifocal ventricular ectopics. The serum potassium concentration was 5.4 mmol litre$^{-1}$ and oral temperature 36.5 °C. At no time did the patient appear hot, nor did his temperature increase.

Serial potassium estimations over the next seven days revealed values always less than 4.4 mmol litre$^{-1}$, and subsequent e.c.g. showed a normal trace with a tachycardia for the first three days. Serial arterial blood analysis showed a persistent acidosis.

Six hours after the cardiac arrest the patient was alert, orientated and talking. On examination of the lungs there were audible ronchi on the left side. Over the next twelve hours the patient's respiratory effort decreased and he became unable to cough and clear his secretions, developing supraventricular tachycardia of 220 beat min$^{-1}$ which was resistant to digoxin. The lungs were ventilated artificially for four days, during which time the patient was given sodium bicarbonate and potassium by infusion to correct the acidosis as indicated (see table I).

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TABLE I. *Administration of sodium bicarbonate to correct acidosis*

| Time after arrest (h) | pH (unit) | | Bicarbonate administered (mmol) | Heart rate (beat min$^{-1}$) |
|---|---|---|---|---|
| 0.5 | 7.17 | | 12.5 | 220 |
| 20 | 7.21 | | 20 | 160 |
| 28 | 7.20 | | | 160 |
| 31 | 7.27 | $F_{IO_2}$ | 20 | 160 |
| 38 | 7.28 | 0.4 | 23 | 150 |
| 48 | 7.41 | 175 ml | | 150 |
| 72 | 7.40 | × 20 per min | | 130 |
| 96 | 7.36 | | | 115 |
| 120 | 7.46 | | | 90 |
| 142 | 7.43 | | | 105 |

Frequent chest physiotherapy was applied and physiotherapy was also required for progressive foot drop. The calves became progressively hypertrophic.

Serum creatinine phosphokinase on the second day was 30 000 i.u. and on day ten was 10 000 i.u. After recovery the patient had a typical Duchenne walk and was able to rise from sitting on the floor only by climbing up his legs. The diagnosis was confirmed by muscle biopsy and e.m.g.

## DISCUSSION

Suxamethonium has previously been reported as being associated with cardiac arrest in pseudohypertrophic muscular dystrophy and prolonged hypertonicity in other cases.

The interesting feature of this patient was the immediate hypertonicity following injection of suxamethonium with a rapidly progressing cyanosis leading to cardiac arrest. This, together with the developing acidosis, brought to mind a possible diagnosis of malignant hyperpyrexia, although the temperature was never greater than 36.5 °C.

The mechanism of the cardiac arrest will remain in doubt. There is a possibility that the arrest was a result of hyperkalaemia, although the highest recorded serum potassium value was 5.4 mmol litre$^{-1}$, or the arrest may have been precipitated by hypoxia following some seven minutes after the rigidity and ensuing cyanosis. Duchenne muscular dystrophy is itself associated with heart defects, but in this case both e.c.g. and cardiac shadows on x-ray were normal. There was, however, a persistent supraventricular tachycardia for 72 h.

The muscle cell abnormality both in muscular dystrophy and malignant hyperpyrexia is unknown and this case shows many of the features of the malignant hyperpyrexia syndrome. Perhaps this should serve as a further warning that muscle relaxants may be hazardous in patients with any form of muscle disorder, including squint and hernia. A history of delayed motor milestones should also be treated seriously, as an indicator of underlying disorder, and thoroughly investigated.

## REFERENCES

Ellis, F. R., and Halsall, P. J. (1980). Malignant hyperpyrexia muscle disease. *Br. J., Hosp. Med.*, 24, 318.

Genever, E. E. (1971). Suxamethonium induced cardiac arrest in unsuspected pseudohypertrophic muscular dystrophy. *Br. J. Anaesth.*, 43, 984.

Tammisto, T., Brander, P., Airaksimen, X., Tonnila, V., and Listola, J. (1970). Strabismus as a possible sign of latent muscular disease predisposing to suxamethonium induced muscular injury. *Farmatsiia*, 19, 126.

## HYPERTONIE ET ARRET CARDIAQUE ASSOCIES AU SUXAMETHONIUM DANS UNE DYSTROPHIE MUSCULAIRE PSEUDO-HYPERTROPHIQUE NON DIAGNOSTIQUEE

### RESUME

Nous rapportons un cas qui a montré beaucoup de similitudes avec le syndrome d'hyperthermie maligne, après injection de suxaméthonium dans un cas non diagnostiqué de dystrophie musculaire pseudohypertrophique (Arran-Duchène).

## NACH SUXAMETHONIUM AUFTRETENDER HYPERTONUS UND HERZSTILLSTAND BEI NICHT BEKANNTER PSEUDOHYPERTROPHISCHER MUSKELDYSTROPHIE

### ZUSAMMENFASSUNG

Wir berichten über einen Fall, der viele merkmale der Malignen Hyperthermie aufwies, und nach Verabreichung von Suxamethonium bei einem Fall von nicht bekannter pseudohypertrophischer Muskeldystrophie (Duchenne).

## SUXAMETONIO ASOCIADO CON HIPERTONICIDAD Y PARADA DEL CORAZÓN EN DISTROFÌA MUSCULAR SEUDO-HIPERTRÓFICA INSOSPECHADA

### SUMARIO

Informamos sobre un caso en que se manifestaron muchos de los rasgos del sindrome de hiperpirexia maligna a raíz de la administración de suxametonio en un caso insospechado de distrofia muscular seudo-hipertrófica (Duchenne).

*Br. J. Anaesth.* (1982), 54, 1333

# USE OF METYROSINE IN THE ANAESTHETIC MANAGEMENT OF PATIENTS WITH CATECHOLAMINE-SECRETING TUMOURS

## *A case report*

L. TRINER, L. BAER, R. GALLAGHER AND S. WEITZMAN

## SUMMARY

Metyrosine 1.5 g daily for 9 days decreased 24-h urine metanephrine concentration by about 60% in a patient with multiple catecholamine-secreting paragangliomas. Despite the considerable inhibition of catecholamine synthesis, this patient exhibited stress-induced sympathetic overactivity, indicated by increases in arterial pressure and serum catecholamine and urine metanephrine concentrations. It is concluded that metyrosine should be introduced early to the preoperative regimen. In this way, optimal inhibitory effect on catecholamine synthesis can be obtained and maintained for a sufficient time to allow catecholamine stores to become as close to normal as possible. Attainment of the optimal therapeutic effect is not clearly defined, but would seem to be best gauged by a combination of clinical tests of sympathetic responses and of suppression of urinary excretion of metanephrines or VMA.

The purpose of preoperative preparation of patients with catecholamine-secreting tumours is to protect them from the effects of an excess of catecholamines and to ensure a safe perioperative course. Adrenergic blocking drugs, such as phenoxybenzamine and propranolol, have been useful in reducing the effects of catecholamine excess before and during operation.

Another approach to the preoperative preparation of patients with catecholamine-secreting tumours would seem to be to decrease the rate of catecholamine synthesis with metyrosine (alpha-methyl-paratyrosine). This tyrosine analogue is an inhibitor of tyrosine hydroxylase, which catalyses the rate-limiting step in catecholamine synthesis, namely the conversion of tyrosine to dihydroxy phenylalanine (dopa). We report the use of metyrosine in the pre- and intra-operative management of a patient with multifocal catecholamine-secreting paragangliomas.

## CASE REPORT

A 53-year-old white male developed labile hypertension in 1970. In 1977, he underwent investigation and functional cervical and abdominal paragangliomas vere diagnosed. Subsequently, the abdominal paraganglioma was removed. The cervical paranganglioma was judged to be inoperable and was treated with radiotherapy. The 24-h urine metanephrine concentration remained increased at 5.5 mg/24 h (normal = < 1 mg/24 h), while the labile hypertension was partially controlled (140–150/90–110 mm Hg) with oral propranolol 20 mg and phenoxybenzamine 10 mg, three times daily.

Four years later, the patient was admitted to hospital for surgical correction of a right inguinal hernia. Labile hypertension was again noted, with marked increases of 24-h urine metanephrine concentrations (fig. 1). X-rays revealed a right rib abnormality and bone scan showed several rib and left femoral "hot spots". Subsequent rib biopsy demonstrated paranganglioma tissue. As the inguinal hernia interfered with walking, it was decided to proceed with surgery.

Oral propranolol 20 mg and phenoxybenzamine 10 mg four times daily were continued and, on the ninth day before surgery, oral metyrosine was added to the regimen. The dose was rapidly increased to 500 mg three times daily. Vital signs were observed closely and sequential 24-h urine samples were collected for metanephrine determinations (fig. 1). When good control of arterial pressure and a substantial decrease in urine metanephrine excretion were achieved, the patient was considered to be

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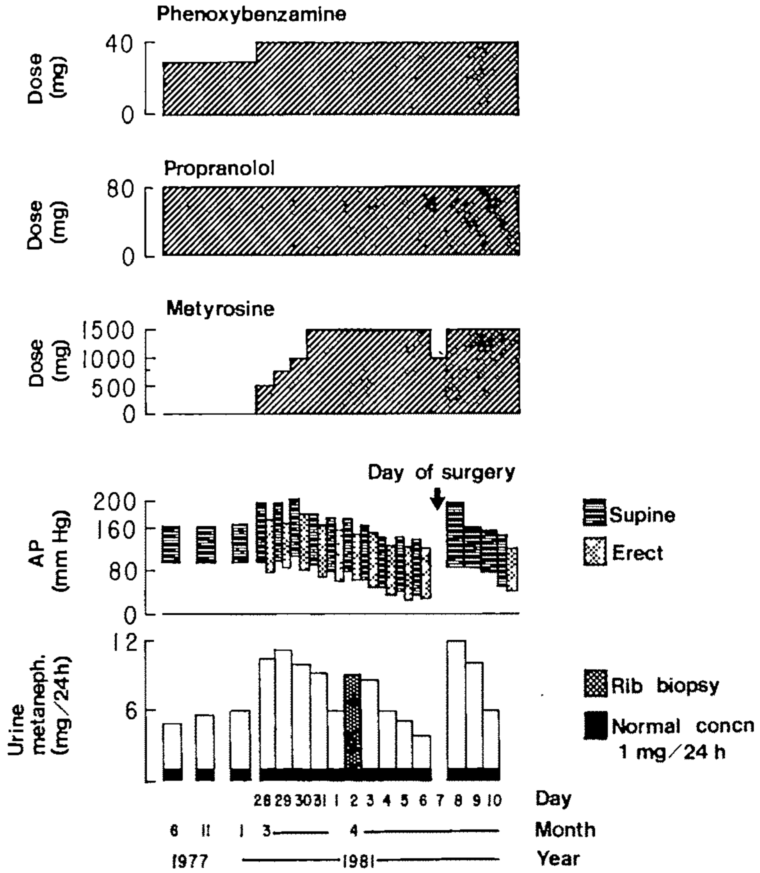

FIG. 1. Medication, arterial pressure and 24-h urine metanephrine concentrations before and during operation.

satisfactorily prepared for surgery.

Premedication consisted of pethidine 75 mg and hydroxyzine 50 mg i.m. Two peripheral intravenous and a radial artery catheter were inserted.

On his arrival in the operating room, the patient's arterial pressure was increased (200–210/90–110 mmHg) and his pulse was 70–80 beat min$^{-1}$. Anaesthesia consisted of a continuous lumbar extradural block with 1.5% carbocaine (total volume, 28 ml). Throughout surgery the level of analgesia remained at T4–T10 and the patient was free of pain and discomfort. Sedation was accomplished with pethidine (total 40 mg i.v.). Arterial pressure remained increased and intermittent sodium nitroprusside infusion was required for its control. Total serum catecholamine concentrations were increased before and markedly during surgery (fig. 2). Urine metanephrine concentrations were also increased for 48 h after operation and then began to decrease (fig. 1). Arterial pressure changes during the period after operation generally followed the changes in urine metanephrines, which apparently reflected an excess of catecholamine release.

The patient had an uneventful postoperative course and was discharged with a continuing regimen of propranolol 20 mg and phenoxybenzamine 10 mg four times daily, and metyrosine 500 mg three times daily.

## DISCUSSION

This report illustrates some of the problems encountered in patients with catecholamine-secreting tumours. It was evident at the time of the patient's admission that he had signs and symptoms of uncontrolled catecholamine excess. Indeed, 24-h urinary

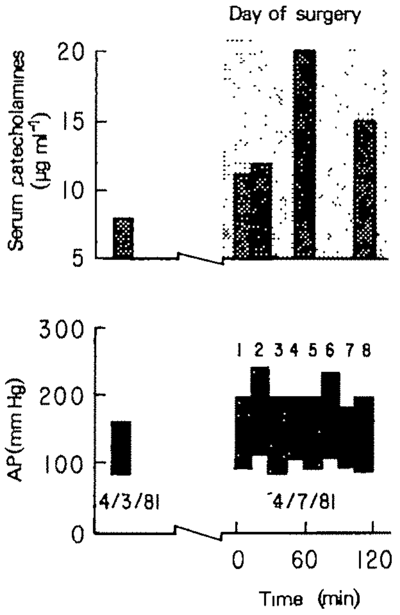

FIG. 2. Serum catecholamine concentrations and arterial pressure before and during surgery: 1 = arrival in operating room; 2 = insertion of extradural catheter (sitting position); 3 = nitroprusside infusion started; 4 = 1.5% carbocaine administered slowly (16 ml), nitroprusside discontinued; 5 = surgery started (T8 level analgesia); 6 = Valsalva manoeuvre, nitroprusside infusion restarted; 7 = response to nitroprusside; 8 = surgery completed.

excretion of metanephrines was greater than noted previously (fig. 1), and the metastatic bone lesions (proved on biopsy) confirmed the likelihood of a recent growth or spread of the functional paragangliomas and indicated the need for more vigorous preoperative preparation. The clinical and laboratory data show that metyrosine provided the means to re-establish control in this patient.

The management of this patient is instructive regarding the attainment of optimal benefit from metyrosine. Despite a 50–60% decrease in urinary metanephrine excretion associated with significant improvement in arterial pressure control, clinical and laboratory evidence of stress-induced sympathetic overactivity was seen on two occasions (fig. 1). The first was related to the performance of a rib biopsy under local anaesthesia. The second episode occurred on the day of surgery. These responses probably represent the effects of catecholamines released from tumour tissues and from peripheral stores.

Our experience indicates that attainment of normal or near normal arterial pressure, heart rate and urinary excretion of catecholamines or metanephrines, under relatively non-stressful conditions, is not a reliable predictive index of the subsequent intraoperative course. It remains to be determined if metyrosine at greater doses and maintained for longer periods would render normal the rate of catecholamine synthesis and prevent release of excess catecholamines during surgery.

A review of the literature indicates that, when used alone or in combination with adrenergic blockade, metyrosine is of value in protecting patients with catecholamine-secreting tumours from the deleterious effects of catecholamine excess (Sjoerdsma et al., 1965; Sjoerdsma et al., 1966; Jones et al., 1968; Bagnall, Salway and Jackson, 1976; Robinson et al., 1977; Hengstmann, Gugler and Dengler, 1979). One would expect that administration of metyrosine before operation should ensure a smoother course during surgery. However, available data do not permit a definitive conclusion (Sjoerdsma et al., 1966; Jones et al., 1968; Tcherdakoff et al., 1972; Bagnall, Salway and Jackson, 1976; Robinson et al., 1977; Bergman et al., 1978; Smith, Aukburg and Levitt, 1978; Hengstmann, Gugler and Dengler, 1979). As a result of our observations, we feel that different degrees of catecholamine synthesis suppression were achieved in the reported studies and this may account for the mixed clinical impressions reported. It is known that the degree of metyrosine inhibition of catecholamine synthesis is dose related and that there is variation in the amount required to achieve a given degree of inhibition (Sjoerdsma et al., 1965; Jones et al., 1968).

We believe that preoperative metyrosine should be introduced early so that the optimal effect can be obtained, usually in 7–10 days (Engelman, 1977) and maintained sufficiently long to achieve as much normalization of catecholamine stores as is possible. While the duration of this period cannot be predicted at present, it can be estimated from the data of Hengstmann and Dengler (1978) that, even with complete inhibition of excess catecholamine synthesis, normalization of catecholamine stores could take from 1 week to 50 days (four to five half-lives). More information is needed regarding the clinical and laboratory criteria most helpful in predicting the attainment of this goal, which presently would seem to be best gauged by a combination of clinical tests of sympathetic responses and the suppression of urinary excretion of metanephrines or VMA.

ACKNOWLEDGEMENTS

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REFERENCES

Bagnall, W. E., Salway, J. G., and Jackson, E. W. (1976). Phaeochromocytoma with myocarditis managed with α-methyl-p-tyrosine. *Postgrad. Med. J.*, **52**, 653.

Bergman, S. M., Sears, H. F., Javadpour, N., and Keiser, H. R. (1978). Postoperative management of patients with pheochromocytoma. *J. Urol.*, **120**, 109.

Engelman, K. (1977). Phaeochromocytoma. *Clin. Endocrinol. Metab.*, **6**, 769.

Hengstmann, J. H., and Dengler, H. J. (1978). Evidence for extratumoural storage of catecholamines in pheochromocytoma patients. *Acta Endocrinol.*, **87**, 589.

—— Gugler, R., and Dengler, H. J. (1979). Malignant pheochromocytoma. Effect of oral α-methyl-p-tyrosine upon catecholamine metabolism. *Klin. Wochenschr.*, **57**, 351.

Jones, N. F., Walker, G., Ruthuen, C. R. J., and Sandler, M. (1968). α-Methyl-p-tyrosine in the management of phaeochromocytoma. *Lancet*, **2**, 1105.

Robinson, R. G., DeQuattro, V., Grushkin, C. M., and Lieberman, E. (1977). Childhood pheochromocytoma: Treatment with alpha methyl tyrosine for resistant hypertension. *J. Pediatr.*, **91**, 143.

Sjoerdsma, A., Engelman, K., Spector, S., and Udenfriend, S. (1965). Inhibition of catecholamine synthesis in man with alpha-methyl-tyrosine, an inhibitor of tyrosine hydroxylase. *Lancet*, **2**, 1092.

————Waldmann, T., Cooperman, L. H., and Hammond, W. G. (1966). Pheochromocytoma: Current concepts of diagnosis and treatment. *Ann. Int. Med.*, **65**, 1302.

Smith, D. S., Aukburg, S., and Levitt, J. (1978). Induction of anesthesia in a patient with an undiagnosed pheochromocytoma. *Anesthesiology*, **49**, 368.

Tcherdakoff, P., Menard, J., Bedrossian, J., Vaysse, Alexandre, J. M., Desmonts, J. M., and Milliez, P. (1972). Alpha-méthyl-para-tyrosine dans le traitment prolongé du phéochromocytome malin et la préparation pré-opératoire du phéochromocytome bénin: étude préliminarie. *J. Urol. Nephrol.*, **78**, 744.

## UTILISATION DE LA METYROSINE DANS LE PROTOCOLE ANESTHESIQUE DE PATIENTS AYANT DES TUMEURS SECRETANT DES CATECHOLAMINES

*A propos d'un cas*

### RESUME

L'utilisation de métyrosine 1,5 mg par jour pendant 9 jours, a diminué la concentration urinaire des 24 h de métanéphrine d'environ 60% chez un patient porteur de paragangliomes multiples sécrétant des catécholamines. Malgré une inhibition considérable de la synthèse des catécholamines, ce patient objectivait une hyperactivité sympathique liée au stress, qui se traduisait par une élévation de la pression artérielle, des catécholamines sériques et de la concentration urinaire de métanéphrine. Nous en concluons que le métyrosine devrait être introduite de façon précoce dans la préparation à l'intervention. De cette façon, on peut obtenir un effet inhibiteur optimal sur la synthèse des catécholamines et le maintenir pendant un temps suffisant pour permettre aux réserves de catécholamines de retrouver une valeur aussi proche que possible de la normale. On ne sait pas encore clairement définir quel est le meilleur effet thérapeutique, mais il semble que celui-ci puisse être au mieux estimé par l-association de tests cliniques à des résponses sympathiques et d'une suppression de l'excrétion urinaire des méthanéphrines ou du VMA.

## DER NUTZEN DES METHYROSIN BEI NARKOSEN VON PATIENTEN, DIE AN TUMOREN MIT KATECHOLAMINAUSSCHÜTTUNG LEIDEN

### ZUSAMMENFASSUNG

Methyrosin 1,5 mg pro Tag 9 Tage lang senkte die 24 h-Urin-Konzentration von Metanephrin um ungefähr 60% bei einem Patienten mit multiplen, Katecholamin sezernierenden Paragangliomen. Trotz der beträchtlichen Hemmung der Katecholamin-Synthese zeigte der Patient eine stressinduzierte sympathische überaktivität, die sich durch einen Anstieg des arteriellen Blutdrucks, sowie der Serum-Katecholamine und des Urin-Metanephrins äusserten. Daraus ist zu schliessen, daß Methyrosin frühzeitig zur präoperativen Behandlung gehören sollte. Auf diese Weise kann eine optimale Hemmung der Katecholamin-Synthese erreicht und genügend lange aufrecht erhalten werden, um die Katecholamin-Vorräte soweit wie möglich zu normalisieren. Wann der optimale therapeutische Effekt erreicht ist, ist nicht klar definiert, scheint aber am besten durch eine Verbindung von klinischen Tests der Sympatikus-Tätigkeit und Supprimierung der urinausscheidung von Metanephrinen oder Vanillinmandelsäuren (VMA) bestimmt werden zu können.

## USO DE METIROSINA EN LA GESTION ANESTESICA DE PACIENTES CON TUMORES QUE SEGREGAN CATECOLAMINA

### SUMARIO

La administración de 1,5 gramos de metirosina diarios por espacio de 9 días disminuyó en aproximadamente el 60% la concentración de metanefrina en la orina en un ciclo de 24 horas, en un paciente con paragangliomas múltiples que segregaban catecolamina. A pesar de la considerable inhibición de la síntesis de catecolamina, este paciente mostró una sobreactividad del sistema simpático inducida por la tensión, que se puso de manifiesto por un aumento de la presión arterial y por la concentración de catecolamina en el suero y en la de mentanefrina en la orina. Se concluye que la metirosina debe introducirse en el régimen preoperativo en sus primeras fases. De esta forma pueden obtenerse y mantenerse los efectos inhibitorios óptimos de la síntesis de la catecolamina durante el suficiente espacio de tiempo para permitir que el almacenamiento de ésta se acerque lo más posible a lo normal. La obtención del efecto terapeútico óptimo no está claramente definido, pero parece que se mediría mejor mediante una combinación de pruebas clínicas de las respuestas del sistema simpático y de supresión de metanefrinas en la excreción urinaria or de VMA.

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# SYSTEMIC REACTION TO SUBARACHNOID INJECTION OF PHENYLEPHRINE

A. FREDRIKSEN

SUMMARY

An adverse reaction is presented. The patient developed a skin rash, hypertension, bradycardia, a ventricular bigeminal rhythm, and signs of ischaemia in the electrocardiogram after subarachnoid injection of phenylephrine 10 mg.

The injection of vasoconstrictors together with a local anaesthetic will prolong the duration of spinal anaesthesia. We use phenylephrine ((-)-1-(m-hydroxyphenyl)-2-methyl-aminoethanol HCl), which has been reported to double the duration of anaesthesia (Moore and Bridenbaugh, 1966). These authors found no systemic response to the added phenylephrine in a retrospective study of 1911 spinal anaesthesias.

## CASE REPORT

A 42-year-old woman was admitted for removal of varicose veins. She was in good general health.

Premedication was with atropine 0.5 mg, pethidine 50 mg and promethazine 50 mg i.m. A lumbar puncture was performed, and aspiration produced clear spinal fluid. Amethocaine 15 mg in a glucose solution with phenylephrine hydrochloride 10 mg was injected.

The patient immediately complained of dizziness. She remained conscious, but seemed withdrawn. A skin rash appeared on the thorax and upper extremities and the mean arterial pressure increased from 105 to 165 mm Hg. The e.c.g. showed premature ventricular contractions in a bigeminal rhythm, and the effective heart rate was 55 beat min$^{-1}$. The cardiac arrythmia responded to lignocaine 100 mg, the arterial pressure returned to normal and the rash gradually disappeared. E.c.g. 10 min after the onset of symptoms showed signs of ischaemia with depression of the ST segment and inversion of the T wave, most prominent in the lateral precordial leads. Five hours later e.c.g. showed no ischaemic changes, and the patient reported no after-effects.

With the patient's consent the drugs given for the operation were given again in the intensive care unit a few days later. E.c.g. was monitored continuously, and an i.v. infusion was established. After no local

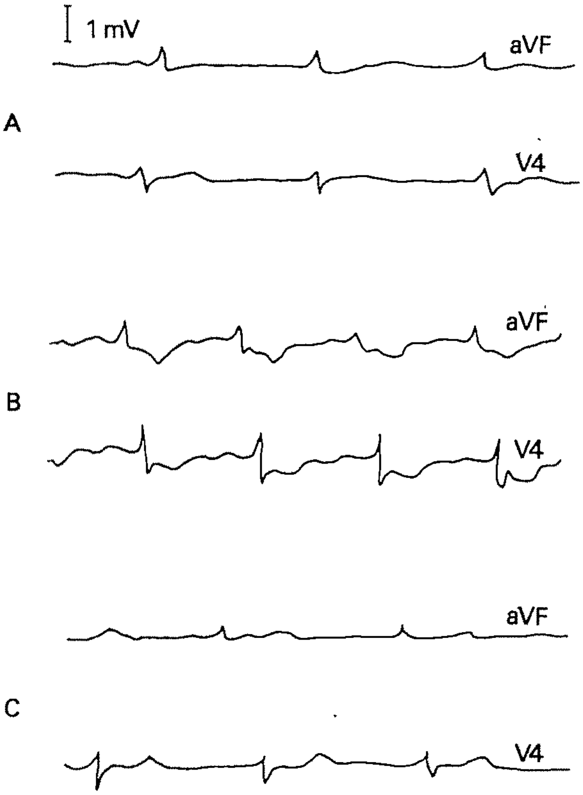

FIG. 1. A: Leads aVF and V4 recorded on admission. B: The same leads recorded 10 min after the adverse reaction. C: The recording made 5 h after the episode. Note marked ST-depression and T inversion in B, indicative of myocardial ischaemia. Paper speed 50 mm s$^{-1}$.

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response was provoked with intracutaneous injections of dilute solutions of amethocaine and phenylephrine, i.v. injections were given. Amethocaine caused no response. After phenylephrine 0.25 mg, however, the patient reported the same feeling of dizziness, but remained alert. Mean arterial pressure increased from 115 to 145 mm Hg, the heart rate was reduced from 90 to 75 beat min$^{-1}$, and a rash developed. Arterial pressure and heart rate returned to normal within 5 min and the rash disappeared. E.c.g. monitoring continued for another 30 min.

## DISCUSSION

Phenylephrine has mainly alpha-adrenergic effects. It causes peripheral vasoconstriction, increased arterial pressure, and reflex bradycardia, while the blood flow to the skin and kidneys is reduced (Eckstein and Abboud, 1962). The drug may be used to treat atrial tachycardia and hypotensive states, and in topical preparations as a mydriatic agent and a nasal decongestant. It has not been reported as causing cardiac arrhythmia when used during halothane anaesthesia (Martindale, 1977). Moore and Bridenbaugh (1966) compared the effects of ephedrine, adrenaline and phenylephrine as additives to the local anaesthetic. They found that the duration of anaesthesia was increased twofold by phenylephrine 5 mg, and by 50% by adrenaline 0.2 mg. Ephedrine had no influence on the duration of block.

There are several reports on systemic effects of topical phenylephrine (Vaugham, 1973; Fraunfelder and Scafidi, 1978; Leopold, 1978), but none from subarachnoid injection. We do not know if our patient's reaction was allergic or toxic. The transient rash may suggest allergy, but allergies to adrenergic substances are rare.

The dose of phenylephrine would be sufficient to cause toxic symptoms. The most likely explanation is that the phenylephrine gained access to the circulation, either by very rapid absorption from the subarachnoid space, or by some degree of i.v. injection.

## REFERENCES

Eckstein, J. W., and Abboud, F. M. (1962). Circulatory effects of sympathomimetic amines. *Am. Heart. J.*, 63, 119.

Fraunfelder, F. T., and Scafidi, A. F. (1978). Possible adverse effects from topical ocular 10% phenylephrine. *Am. J. Ophthalmol.*, 85, 862.

Leopold, I. H. (1978). The phenylephrine saga,—a drug dilemma. *Am. J. Ophthalmol.*, 85, 572.

Martindale, E. (1977). *The Extra Pharmacopeia*, 27th edn, p. 27. London: The Pharmaceutical Press.

Moore, D. C., and Bridenbaugh, L. D. (1966). Spinal (subarachnoidal) block. *J.A.M.A.*, 195, 907.

Vaughan, R. W. (1973). Ventricular arrhythmias after topical vasoconstrictors. *Anesth. Analg. (Cleve.)*, 52, 161.

## REACTION SYSTEMIQUE A UNE INJECTION SOUS-ARACHNOIDIENNE NEOSYNEPHRINE

### RESUME

Nous présentons ici une réaction délétère. Le patient a objectivé une éruption cutanée, une poussée hypertensive, une bradycardie, un bigéminisme ventriculaire et des signes électrocardiographiques d'ischémie après une injection sous-arachnoïdienne de néosynéphrine 10 mg.

## DIE SYSTEMISCHE REAKTION AUF DIE ARACHNOIDALE INJEKTION VON PHENYLEPHRIN

### ZUSAMMENFASSUNG

Es wird eine ungünstige Reaktion beschrieben. Der Patient entwickelte eine Hautrötung, Blutdruckabfall, Bradykardie, einen ventrikulären Bigeminus-Rythmus und Ischämiezeichen im EKG nach der subarachnoidalen Injektion von Phenylephrin 10 mg.

## REACCIÓN SISTÉMICA A UNA INYECCIÓN SUBARACNOIDAL DE FENILEFRINA

### SUMARIO

Se presenta una reacción adversa. El paciente desarrolló una erupción cutánea, hipertensión, bradicardía, un ritmo ventricular bigeminal y señales de isquemia en su electro-cardiograma después de una inyección de 10 mg de fenilefrina subaracnoidal.

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# ANAESTHETIC MANAGEMENT OF ACUTE LARYNGEAL TRAUMA

L. M. FLOOD AND B. ASTLEY

## SUMMARY

Three patients suffering acute laryngeal trauma illustrate problems of missed diagnosis and airway management confronting anaesthetists. A 55-year-old man suffered multiple injuries, including a supraglottic laryngeal fracture which was not diagnosed during administration of a subsequent general anaesthetic. The diagnostic delay compromised any reconstructive surgery. Two 26-year-old males suffered laryngeal fractures, but tracheal intubation for reconstruction and tracheostomy was successful. Guidelines for management are suggested.

Acute laryngeal trauma and the consequent difficulty in maintaining an adequate airway demand of the anaesthetist skills in both diagnosis and subsequent management. When associated with major head, neck and maxillofacial trauma, the closed laryngeal injury may pass unnoticed on initial assessment in the casualty department, only to be recognized by the anaesthetist during tracheal intubation or even in the recovery period. Early treatment to protect the airway and avoid residual impairment of laryngeal function is vital and it is therefore imperative to seek and exclude such injuries during laryngoscopy at intubation and to be aware of the immediate problems in management of the airway which may occur.

## CASE REPORTS

### *Patient 1*

A 55-year-old male suffered fractures of his mandible and left wrist following head-on collision with a lorry. In a local hospital, both fractures were reduced with internal fixation under general anaesthesia. There was no apparent difficulty with tracheal intubation and no laryngeal injury was noted.

Five days after operation the patient was fevered, complained of dysphagia, haemoptysis and stridor on lying supine, although his voice was normal. On his transfer to this hospital computerized tomograms and x-rays revealed a supraglottic laryngeal fracture and a longitudinal tear of the posterior pharyngeal wall (figs 1, 2). Laryngoscopy and elective tracheotomy were performed under general anaesthesia induced with thiopentone 350 mg, in

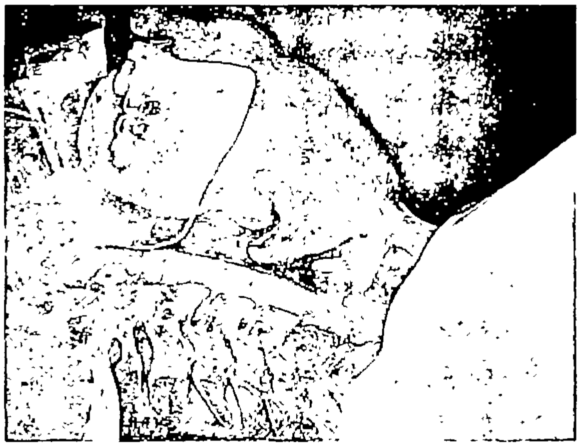

FIG. 1. Xerogram of lateral neck, supine, showing fracture of the hyoid, with a deep tear through the vallecula and consequent posterior displacement of the epiglottis.

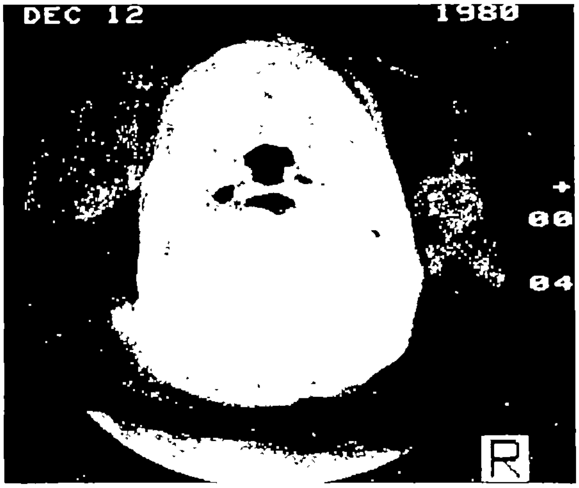

FIG. 2. C.T. scan of neck showing displacement of epiglottis, restricted airway and widening of the vallecular sulcus.

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semi-erect position, after 5 min of preoxygenation, and maintained with halothane in a mixture of nitrous oxide in oxygen. The patient breathed spontaneously via a Magill system. As the vocal cords were easily visible on lifting the epiglottis, suxamethonium 100 mg was given i.v. and the trachea was intubated (8-mm cuffed oral endotracheal tube).

Laryngoscopy revealed deep tears through the vallecular sulcus and posterior pharyngeal wall. Because of delay in presentation and consequent sepsis the injuries were managed conservatively and surgery was limited to fashioning of a tracheostomy. A McMichael fine-bore naso-gastric tube was passed and antibiotic therapy commenced.

The tracheostomy was retained to allow access to the airway for general anaesthesia as further operations were necessary to reduce the mandible and wrist. The patient was now comfortable and serial x-rays showed progressive restoration of the airway. At 6 weeks the tracheostomy was corked and withdrawn at 10 weeks. There was no residual damage to airway or voice.

*Patient 2*

A 26-year-old male was admitted following a road traffic accident. Preliminary examination revealed scalp injuries and superficial injuries of the neck. Over the next 7 h there developed gross surgical emphysema of the neck, stridor when supine, and pain and tenderness over the larynx.

The patient underwent laryngoscopy, exploration of the neck, and tracheotomy. Anaesthesia was induced with halothane in nitrous oxide in oxygen. However, the patient became excited with increasing stridor, and thiopentone 200 mg allowed successful ventilation of the lungs via a mask. Suxamethonium 100 mg was given and a 6-mm nasal cuffed endotracheal tube was inserted.

Direct laryngoscopy and exploration of the neck revealed a vertical midline fracture separating the thyroid alae, with a horizontal tear of the laryngeal mucosa along the right false cord, exposing the arytenoid cartilage. The mucosal tear was sutured and the thyroid cartilage fracture reduced and fixed with steel wire sutures. A tracheostomy was fashioned and McMichael naso-gastric tube passed.

Six days after operation the patient commenced oral feeding. At 20 days direct laryngoscopy showed the right arytenoid to have satisfactory mucosal cover. At 24 days the tracheostomy tube was withdrawn and at 3 months a final endoscopy showed fully mobile cords with no stenosis, while the voice and airway were normal.

*Patient 3*

A 26-year-old male was punched on the throat. On admission to hospital he complained of hoarseness, dysphagia and haemoptysis. There was no stridor. Surgical emphysema of the neck produced loss of the normal laryngeal prominence. Mirror examination revealed some posterior displacement of the epiglottis.

Laryngoscopy, open exploration of the larynx and tracheotomy, under general anaesthesia, followed. After preoxygenation the patient received an inhalation induction with oxygen, nitrous oxide and halothane. When the patient was sufficiently anaesthetized to allow manual ventilation of the lungs with bag and mask, suxamethonium 100 mg i.v. produced relaxation and a 9-mm red rubber Magill cuffed oral tube was introduced to the trachea.

Laryngoscopy showed swelling of the left arytenoid, but intact vocal cords. Exploration of the neck revealed a vertical midline crack down the laryngeal prominence, without damage to the underlying anterior commissure and this fracture was splinted with steel wire. A horizontal tear through the cricotracheal membrane had produced partial laryngo–tracheal separation but was closed satisfactorily in layers. A naso-gastric tube was inserted.

After 9 days the tracheostomy tube was corked and on the 12th day, withdrawn. Direct largyngoscopy at 4 months showed no abnormality and the voice was normal.

## DISCUSSION

In major trauma, laryngeal injury may pass unnoticed in initial assessment. As illustrated in patient 1, at the time of intubation the anaesthetist has the opportunity to visualize the laryngeal lumen and prevent missed diagnosis. In this patient the more obvious major injuries, facial trauma and blood in the airway proved a distraction. In the second patient, the superficial neck injuries were noted, but the diagnosis was not made for some hours.

The possibility of laryngeal injury should be suspected in all victims of major trauma, especially in road traffic accidents, assault or sporting injury. Symptoms include local pain and dysphagia, hoarseness or haemoptysis. Examination may reveal superficial injuries to the neck and stridor. Increased inspiratory effort, as shown by tracheal tug and suprasternal and intercostal recession, will worsen surgical emphysema. Cyanosis alone is an unreliable index of oxygenation, but hypercarbia produces restlessness and irritability.

Where time allows assessment is aided by mirror examination (indirect laryngoscopy) to assess cord mobility and integrity of the laryngeal lumen. A lateral soft tissue x-ray of the neck and cervical spine may reveal bony or cartilaginous injury. Xeroradiography proved especially useful in patient 1, demonstrating soft tissue injuries. CAT scanning can reliably diagnose fractures of the thyroid cartilage or cricoid ring and assess airway patency (Mancuso and Hanafee, 1979).

Four varieties of laryngeal injury are encountered (Bryce, 1978). In supraglottic laryngeal fracture, as in patient 1, the epiglottis and laryngeal inlet is displaced posteriorly and the vocal cords may be spared. In cricotracheal separation the larynx and trachea are distracted and possibly subluxated, as illustrated in patient 3. Complete separation is usually immediately fatal (Le Jeune, 1978). Commonly a vertical midline fracture will damage the anterior commissure and separate the thyroid alae as in patients 2 and 3. A comminuted fracture, or shattering of the laryngeal skeleton, is found in the older, calcified and rigid larynx.

With the diagnosis established on initial assessment, or at tracheal intubation, the priority is maintenance of the airway. Conservative treatment is hazardous as laryngeal oedema may rapidly progress, although humidified oxygen, steroids and antibiotic prophylaxis may help.

In the cases presented general anaesthesia was required to evaluate the injuries by endoscopy, explore the neck and repair mucosal and cartilaginous injuries and fashion a temporary tracheostomy. Intubation was successfully performed on the unconscious patient in each case.

Hazards which may be encountered on intubation include:

(a) Associated maxillofacial injuries and displacement of teeth, bone or blood into the upper airway, as in patient 1.

(b) Injury to the cervical spine, at risk on neck extension during intubation.

(c) Complete cricotracheal separation. Symptoms may initially be mild because of the splinting action of the strap muscles. However, paralysis may cause distraction and subluxation of the larynx and trachea, making intubation impossible. In retrospect, use of suxamethonium in patient 3 carried some risk.

(d) Supraglottic laryngeal fracture, producing detachment and posterior displacement of the epiglottis, when the patient is supine. As in patient 1, the Mackintosh laryngoscope blade inserted into the vallecula can elevate the tongue but not the detached supraglottis. Only on elevating the epiglottis was the laryngeal lumen revealed.

(e) Surgical emphysema was not marked, except in patient 3, but may make neck extension difficult and proceed to mediastinal emphysema. None of the patients had penetrating injuries, which can produce air embolism into the great veins of the neck (Vaughan, 1971). A tension pneumothorax is especially dangerous where IPPV is in use.

Alternatives to tracheal intubation on the unconscious patient include tracheotomy or per nasal intubation under local anaesthesia.

Preliminary tracheotomy under local anaesthesia is recommended where airway obstruction is severe, as shown by marked stridor at rest, and use of accessory muscles of respiration (Verrill, 1963). Preoxygenation with 80% helium and 20% oxygen (density one-third that of air) is helpful. Infiltration with lignocaine and adrenaline anaesthetizes the distribution of the superficial cervical plexus, but is used sparingly to avoid diffusion to the recurrent laryngeal nerves, consequent paralysis and further airway deterioration. Preliminary tracheotomy was avoided, however, as stridor was not severe in any case and the procedure on a restless, apprehensive patient with a compromised airway, hypoxia and distended neck veins, is more fraught than the elective procedure performed where endotracheal intubation has been possible.

Nasal intubation is possible under local anaesthesia using Moffat's solution 5 ml (1 ml of adrenaline 1 in 1000; 2 ml of 10% cocaine solution; 2 ml of bicarbonate solution) in the nose and, once the tube is in the nasopharynx, instilling lignocaine 4% to the lumen, anaesthetizing as the tube advances.

Intubation of the anaesthetized patient remains the ideal, however, and was successful in the patients presented. In each case the neck was, nonetheless, infiltrated with lignocaine and the surgeon gowned, lest an emergency tracheotomy be necessary during induction of anaesthesia. Transtracheal insufflation with an i.v. cannula as an emergency method of oxygenation may be performed. Suitable apparatus (Clarke and Cochrane,

1975) was to hand in all cases. Although fibreoptic bronchoscopy was available, its use requires considerable skill (Mulder, Wallace and Woolhouse, 1975).

Premedication was avoided. Atropine may produce cerebral stimulation and so increase oxygen requirements. Opiates suppress breathing and protective laryngeal reflexes (Carson et al., 1973). After preoxygenation, with the patients suitably positioned to minimize stridor, anaesthesia was induced i.v. in patient 1 and by inhalation induction in the patients 2 and 3. The latter method is recommended where there is doubt about the integrity of the airway, whereas in patient 1 the nature of the injury was well established before anaesthesia. In patient 3 induction was trouble-free, although in patient 2 i.v. thiopentone was required. Suxamethonium was withheld until the anaesthetist was certain the lungs could be inflated by manual ventilation and that intubation was possible (Atkinson, 1976).

A generally conservative approach to reconstruction proved most successful. In patient 1, infection and necrosis as a result of the delay in diagnosis prevented primary closure. Healing by secondary intention was excellent. Surgical reconstruction is generally required in penetrating injuries, less so in the closed laryngeal trauma of traffic accidents, and rarely in other blunt trauma (Maran et al., 1981).

Acute closed laryngeal injury is rarely reported (Seed, 1971). Its recognition may be difficult in the presence of major trauma, but a missed diagnosis may produce an unexpected airway obstruction or residual functional impairment such as dysphonia, stenosis and spillover. It therefore behoves the anaesthetist to suspect and exclude such injury and be prepared for the problems with airway management which may arise.

## ACKNOWLEDGEMENTS

We thank Mr H. R. Grant, Consultant Otolaryngologist, Royal Ear Hospital, University College Hospital, for allowing us to report on these patients under his care and Dr P. J. Verrill, Consultant Anaesthetist, University College Hospital, for his assistance and advice in preparation of the paper. Our thanks are also due to Miss E. M. Higgins for typing the manuscript.

## REFERENCES

Atkinson, R. S. (1976). *Recent Advances in Anaesthesia and Analgesia*, 12, 44.

Bryce, D. (1978). *Recent Advances in Otolaryngology*, 5, 171. London: Churchill Livingstone.

Carson, I. W., Moore, J., Balmer, J. P., Dundee, J. W., and McNabb, T. G. (1973). Laryngeal competence with ketamine and other drugs. *Anesthesiology*, 38, 128.

Clarke, S. W., and Cochrane, C. M. (1975). Emergency tracheostomy. *Practitioner*, 215, 340.

Le Jeune, F. E. (1978). Laryngotracheal separation. *Laryngoscope*, 88, 1956.

Mancuso, A. A., and Hanafee, W. N. (1979). Computed tomography of the injured larynx. *Radiology*, 133, 139.

Maran, A. G. D., Murray, J. A. M., Stell, P. M., and Tucker, A. (1981). Early management of laryngeal injuries. *J. R. Soc. Med.*, 74, 656.

Mulder, D. S., Wallace, D. H., and Woolhouse, F. M. (1975). The use of the fibreoptic bronchoscope to facilitate endotracheal intubation following head and neck trauma. *J. Trauma*, 15, 638.

Seed, R. F. (1971). Traumatic injury to the larynx and trachea. *Anaesthesia*, 26, 55.

Vaughan, R. S. (1971). Anaesthesia for open soft tissue injuries of the neck. *Anaesthesia*, 26, 225.

Verrill, P. J. (1963). Anaesthesia in upper respiratory tract obstruction. *Br. J. Anaesth.*, 35, 237.

## CONDUITE A TENIR POUR L'ANESTHESIE DES SUJETS PRESENTANT UN TRAUMATISME LARYNGE AIGU

### RESUME

Trois patients souffrant de traumatisme aigü du larynx illustrent les problèmes de non-dépistage et de contrôle des voies aériennes auxquels les anesthésistes se trouvent confrontés. Un homme de 55 ans a été victime de traumatismes multiples, dont une fracture laryngée supraglottique qui est passée inaperçue lors de l'administration conséquente d'une anesthésie générale. Le retard au diagnostic a empêché toute chirurgie reconstructrice. Deux hommes jeunes de 26 ans ont été victime de fractures laryngées, mais l'intubation trachéale pour plastie et trachéotomie a été couronnée de succès. Nous suggérons quelques grandes lignes de traitement.

## DAS VORGEHEN DES ANÄSTHESISTEN BEIM AKUTEN KEHLKOPFTRAUMA

### ZUSAMMENFASSUNG

Drei Patienten, die ein akutes Kehlkopftrauma erlitten, machen die Probleme anschaulich, die mit nicht erfolgter Diagnose und fehlender Behandlung der Atemwege einhergehen. Ein 55-jähriger Mann mit Polytrauma hatte auch eine Kehlkopffraktur, die bei der später erfolgten Allgemeinnarkose nicht erkannt wurde. Die Verzögerung der Diagnostik machte eine operative Rekonstruktion unmöglich. Zwei 26-jährige Männer erlitten eine Kehlkopffraktur, die endotracheale Intubation zur Rekonstruktion und Tracheotomie gelang jedoch. Es werden Richtlinien fürs Vorgehen vorgeschlagen.

## CONTROL ANESTÉTICO DE TRAUMAS LARÍNGEOS AGUDOS

### SUMARIO

Se da una ilustración de los problemas de diagnósticos erróneos y control de las vías respiratorias a que se enfrentan los anestesistas con tres pacientes que padecían de traumas laríngeos agudos. Un hombre de 55 años de edad sufrió lesiones multiples, inclusive una fractura laríngea supraglótica que no fue diagnosticada durante la administración de un anestético general subsecuente. La demora en el diagnóstico comprometió toda cirujía de reconstrucción. Dos hombres de 26 años de edad sufrieron fracturas laríngeas, pero la intubación de reconstrucción y la traqueotomía tuvieron éxito. Se sugieren pautas de control.

*Br. J. Anaesth.* (1982), 54, 1345

# BOOK REVIEWS

*Problems in Anaesthesia—A Case Study Approach.* By I. Ravin. Published by Little, Brown & Co. Price $16.50.

From the foreword it seems this contributed volume is considered to be an introductory text for "beginning students". The statement is made that "discussion based on actual clinical care problems orients theoretical presentations to directly relevant subjects". The problem-oriented approach is achieved by presenting a series of case histories.

Most chapters follow a similar format, with a case history often describing horrendous events in the operating room, followed by relevant questions on these events ("list seven causes for the hypotensive episodes described in the case report" or "what is the final common pathway of shock in the dog model?"), after which there is discussion. The discussion topics naturally are grouped to provide relevance to the chapter titles, such as "Differential diagnosis of apnoea", "Differential diagnosis of hypercarbia", "Differential diagnosis of hypotension..." etc. Later in the book the differential diagnosis theme gives way to more conventional chapters on paediatric anaesthesia, renal disease, pharmacology of local anaesthetics, etc—but each chapter still retains its case report, no doubt to maintain direct relevance.

Used sparingly, anecdotes undoubtedly enliven—readers of the earlier editions of Samson Wright will surely never forget the footnotes! However, in this book the case anecdotes are often irritatingly pedantic, describing mundane happenings such as the patient being transported to the operating room at 7.10 a.m., or illustrate seriously deficient anaesthetic and surgical management. Some of the clinical situations depicted are so complex that it must be impossible for a new recruit in anaesthesia to pick out important points in the discussion; some of the discussions are as fragmented as the preceding case history is complex. The diagnosis of malignant hyperpyrexia as one of 10 causes of apnoea seems a little far-fetched.

It is difficult to believe that this approach will reduce "learning anxieties" by "pitching *the students* into complexities of clinical anaesthesia". The book contains much factual information which would be appreciated by the more experienced anaesthetist, although the format adopted could prove to be distracting.

*F. R. Ellis*

*Anaesthesia in Otolaryngology and Ophthalmology,* 2nd edn. Edited by John C. Snow. Published (1982) by Appleton-Century-Crofts, New York. Pp. 278; illustrated; indexed. Price £19.90.

Anaesthesia for ear, nose and throat and ophthalmic surgery usually falls within the province of the "general" anaesthetist, yet any surgeon working in these fields will testify to the necessity of having the services of an anaesthetist who is aware of their special problems. It is as true of these subjects as any that the final result may sometimes depend on the skills of the anaesthetist in addition to those of the surgeon. There is not a great choice of literature on these topics and a new text on the subject is potentially valuable.

The author of this book is Professor of Anesthesiology at Boston, Massachusetts, and he also practises at the Massachusetts Eye and Ear Infirmary. This is the second edition, although the first to be made available in the United Kingdom. In his preface Professor Snow states that he wishes to present anaesthetic problems, discuss the management of anaesthetic techniques and provide a bibliography for further reading. It is hoped that the book is of relevance to clinical and resident anaesthesiologists and also nurse anaesthetists. It is perhaps the very breadth of readership which he hopes to address which has resulted in the shortcomings of this book, for these are several and they are serious.

The first and lasting impression is the American-orientated approach and style of writing. The vocabulary and syntax is very different from the average United Kingdom text. The language is turgid and in places hard to understand. However, this is a point that should not be laboured upon, other than to regret the apparently increasing divergence of British and American literature which serves to detract from the message contained therein. Inevitably the trans-Atlantic approach carries over into other areas. The extensive use of barbiturates for premedication would be regarded as unacceptable and out-dated in the United Kingdom, as would the advocacy of the use of spontaneous breathing with assisted ventilation.

A major criticism lies in the layout of the book. It is divided into four sections, the first and last being entitled "General Considerations" and "Complications and Special Procedures" respectively. The considerations are sufficiently general as to include the pharmacology of most anaesthetic agents, whether or not they may be recommended as being relevant to anaesthetic practice in these fields. Chapters in the section on complications include electrocardiography, pollution, fires and electrical hazards, medico-legal aspects of anaesthesia and cardiopulmonary resuscitation. Whilst these are subjects with which an anaesthetist at any level ought to be familiar, a text book on specialist anaesthesia is hardly the most appropriate place to discuss or learn about such problems, particularly as no attempt is made to apply them to the operations in question. The effect has been to change what might have been a short and relevant book into a longer, more expensive and less immediately useful one.

The second and third sections deal with the subject matter of the book. The presentation of anaesthetic problems is quite good as far as it goes, but is not comprehensive. Much is made of the surgical details of every operation, while there is little mention of the management of preoperative medical or other problems commonly found in such patients. Local analgesia is frequently recommended as the method of choice, but seldom is any attempt made to determine which patients will do better with local and which with general. Indeed, throughout the whole book one receives the impression that patients were more of an abstract concept than fellow human beings. The detailed management of anaesthetic techniques in the true sense is hardly discussed at all. The techniques are described in cook-book fashion and whilst undoubtedly safe and practical in the author's hands, few reasons are given for the particular choice made, and little about the underlying principles. This may sound a more serious citicism than it really is, as one has to accept that for many operations differences in technique are essentially minor and inconsequential. However, the authors reveal little about the subtleties of anaesthetic management that make all the difference between merely adequate anaesthesia and the really good anaesthetic which gives the surgeon the best possible operating conditions and also lays the foundation for a calm and tranquil recovery.

Anaesthesia in emergency cases is particularly poorly covered. There is nothing on the management of upper respiratory tract obstruction, and other problems in these fields are dealt with in a rather general way. Many would feel that the recommended technique for dealing with re-bleeding following adenotonsillectomy is distinctly hazardous and one doubts whether Sellick would recognize his crush (*sic*) induction. Surely the most important message the super-specialist can pass on to the less experienced is that of how to deal with the less common but nevertheless life-threatening emergencies.

Lengthy descriptions of common operations and their complications are given, whilst treatment of newer techniques is much more sketchy. While this approach may be reasonable in terms of the frequency in which these operations are done it limits the usefulness of the book as an authoritative reference work. It makes no attempt to be a comprehensive review of the subject, and it is supported by bibliographies rather than detailed references. Even from these sources different conclusions could be drawn than those the author infers.

For the clinical anaesthetist the narrowness of the approach and the failure to give sound advice on life-threatening conditions will cause the book to have little appeal, and similarly it cannot be recommended for examination candidates. Most of the subject is better and more relevantly covered elsewhere, and this book will not remove the need for reading review articles and case reports if one wishes to obtain a balanced view of anaesthesia for otolaryngology and ophthalmology.

*A. K. Adams and A. P. G. Beechey*

*Recent Advances in Anaesthesia and Analgesia*, vol. 14. Edited by R. S. Atkinson and C. Langton Hewer. Published by Churchill Livingstone. Pp. 182; illustrated; indexed.

The publication of the 14th volume of this series 50 years after the first is marked by a most interesting chapter from Dr Langton Hewer describing the evolution of the book. It is doubtful if any of the newer books devoted to similar reviews will survive as long as the *Recent Advances*-series. However, it is opportune to examine volume 14 to see how well it is surviving after half a century.

The book consists of 10 chapters devoted to anaesthesia and cardiovascular diseases, metabolism and toxicity of volatile anaesthetic agents, biotransformation of i.v. anaesthetic agents, hypersensitivity reaction, anaesthesia for day-case surgery, blood transfusion, awareness during surgical operations, the relief of postoperative pain, extradural and intrathecal narcotics and chronic pain. The majority of the topics are succinctly reviewed and make admirable reading for candidates for the final F.F.A.R.C.S. examination. Some authors are not content merely to offer a description of the present state of knowledge, but also speculate about future developments. This is particularly noticeable in a thoughtful article by Dr Bullingham and colleagues on extradural and intrathecal opiates.

The editors should consider protecting the readers from the excessive zeal of certain authors in supporting the text with vast reference lists. The value, and even validity, of some of the references quoted is open to dispute and more selection with regard to quality rather than quantity would be appropriate. Inevitably, minor mistakes occur in both the text and the referencing system, but they do not seriously detract from the book.

I have no doubt that, with the judicious selection of topics and appropriate authors by the editors and their successors, the *Recent Advances* series will achieve its centenary. It still sets the standards by which the young pretenders must be judged.

*G. M. Hall*

*Current Topics in Anaesthesia, 6: Anaesthesia in Patients with Ischaemic Heart Disease.* By David C. Chung. Published by Edward Arnold. Pp. 178; illustrated; indexed. Price £14.00.

This monograph is written by an anaesthetist with a major interest in cardiothoracic surgery at the University of Western Ontario. The book is composed of four sections comprising an introduction; a discussion of the physiology and pharmacology of the coronary circulation; a description of the anaesthetic management of patients with ischaemic heart disease and an outline of some of the problems associated with treatment of these patients, including use of $\beta$-blockers, digitalis toxicity and artificial pacemakers.

The author acknowledges in his preface that much of this text is based on a series of lectures to "house-staff" and this is manifest throughout by wide variation in style and balance of content. This lack of uniformity may be illustrated by the following random selection: the use of 12 figures depicting electrocardiograms in the section devoted to pacemaking, but none in a rather inadequate section devoted to arrythmias and their treatment; 16 pages devoted to digitalis toxicity, but only three to postoperative management; a detailed description of measurement of PEP in the section devoted to monitoring, but no mention of urinary output, and paragraphs which are discursive and imprecise (although ideal for verbal communication) coexisting with economical scientific composition.

Dr Chung is to be congratulated on attempting the well-nigh unattainable—to cover an enormously wide field in a short text for a statedly catholic audience. Unfortunately for the success of this book, there are several other recent publications which cover similar areas and which can be recommended for the trainee anaesthetist.

*G. Smith*

*Code Pink: A Practical System for Neonatal Perinatal Resuscitation.* Edited by Anne Marie Dazé and John W. Scanlon. Published by University Park Press, Baltimore. Pp. 154; illustrated; indexed. Price £11.50.

"Code Pink" is the name chosen at the Columbia Hospital for Women, Washington D.C., U.S.A., for the two-person resuscitation team called to every high risk delivery and to all infant cardiopulmonary emergencies. This little book has been written mainly by members of that hospital, and of the Georgetown University School of Medicine, as a primer on the practical aspects of neonatal/perinatal resuscitation.

The first chapter contains a theoretical review of aspects of perinatal asphyxia, including normal methods of fetal oxygenation, anaerobic metabolism and the effects of cerebral asphyxia on the developing brain. This is followed by chapters on practical aspects of fetal monitoring before and during labour and the diagnosis and nursing management of intrapartum obstetric emergencies. The second half of the book is concerned with management of the asphyxiated newborn, resuscitation and transport, including temperature control.

The book is aimed primarily at nurses, medical students and residents, and it is probably more suitable for the first two categories of reader than the last. There is no mention of the complications of amniocentesis and the clinical value of some of the techniques described is not made clear. Surgical causes of neonatal hypoxia are omitted. Most topics are covered at a fairly superficial level, and there is inadequate detail to allow the reader to deal safely with emergencies such as gastric aspiration. Some of the techniques described and pieces of equipment used are clearly parochial, but nevertheless the advice offered is generally sound. The endotracheal tube sizes recommended are worryingly large, although the authors do recommend that they should not be tightly fitting. It is refreshing to read that "brief exposure to 100% oxygen will in no way result in . . . toxicity."

Some chapters are well referenced, and others not at all. Standard International Units are not given, and the suggestion that resuscitation skills can be learnt from animal models would not receive much support in the U.K. This little book will nevertheless provide a useful starting point for medical students and others who wish to learn more about this important topic.

*D. J. Hatch*

### OTHER BOOKS RECEIVED

*USP DI 1983.*
*Vol. 1 Drug Information for the Health Provider;*
*Vol. 2 Advice for the Patient.* Published by The United States Pharmacopeial Convention, Inc. 12601 Twinbrook Parkway, Rockville, Maryland 20852.

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# Der Anaesthesist

**Mit vierteljährlichem Sonderteil**
*Regional-Anaesthesie*

Organ der Österreichischen Gesellschaft für Anaesthesiologie,
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